



Neurodevelopmental dimension

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1. Context and hypothesis

cohorte French Minds

Identifier les dimensions trans ou a-nosographiques / formes cliniques homogènes

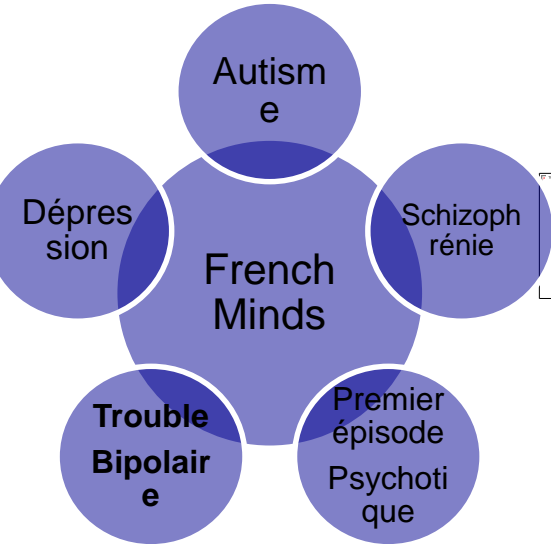
CATÉGORIES DIAGNOSTIQUES EXISTANTES

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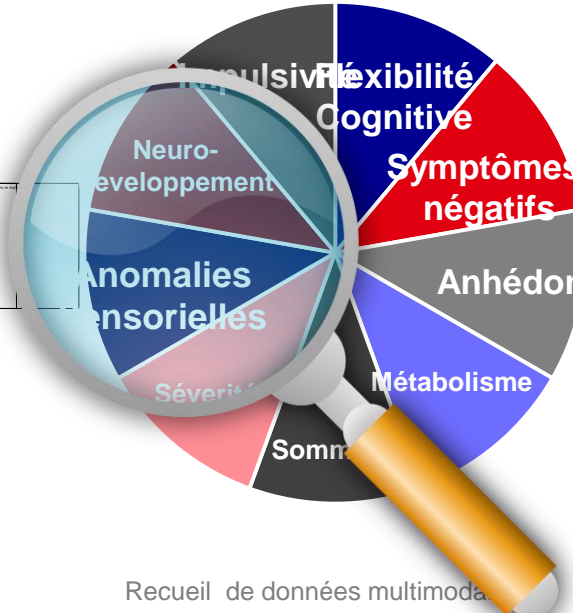
10 DIMENSIONS TRANSNOSOGRAPHIQUES



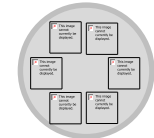
FORMES CLINIQUES HOMOGENES



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Sous-groupes homogènes
Définis cliniquement et biologiquement et qui peuvent être traités avec des traitements basés sur des mécanismes



3

Recueil de données multimodales (cliniques, cognitives, numériques et biologiques)

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Hypothesis

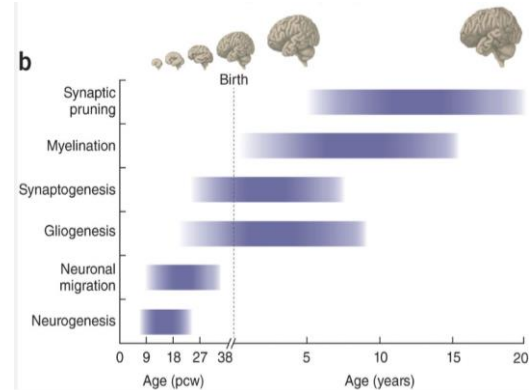
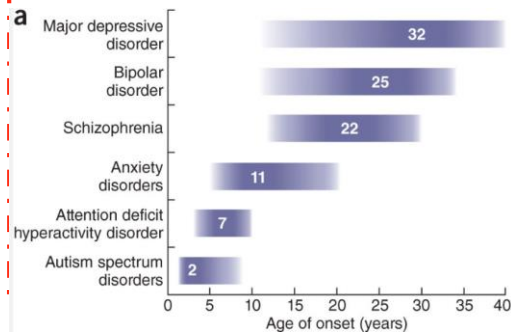
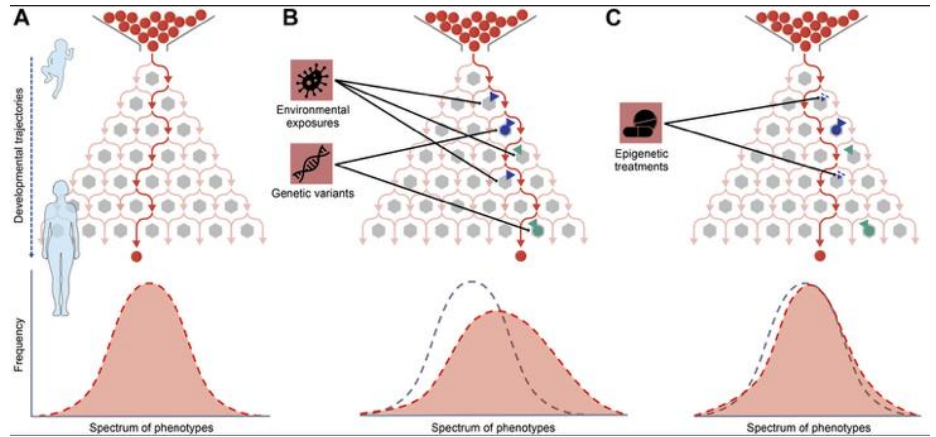


The neurodevelopmental hypothesis as a stratification perspective in mental disorders?

Hypothesis

Neurodevelopmental paradigm

1. Developmental trajectory: linear or non-linear progression over time
2. Period of vulnerability in relation to the timing of the development of each functional structure
3. Dynamic interaction between systems: how the disruption of one system affects the others
4. Leads to different phenotypes



State of the art

Biological Psychiatry



Where do neurodevelopmental conditions fit in transdiagnostic psychiatric frameworks? Incorporating a new neurodevelopmental spectrum

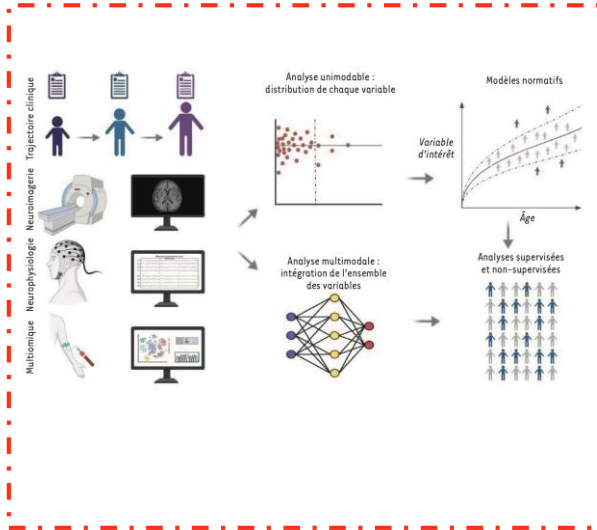
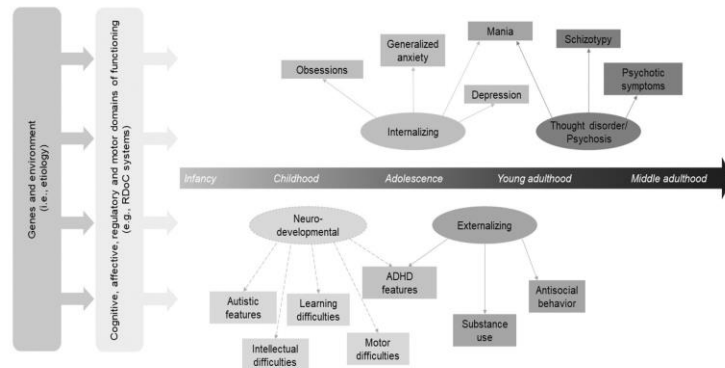
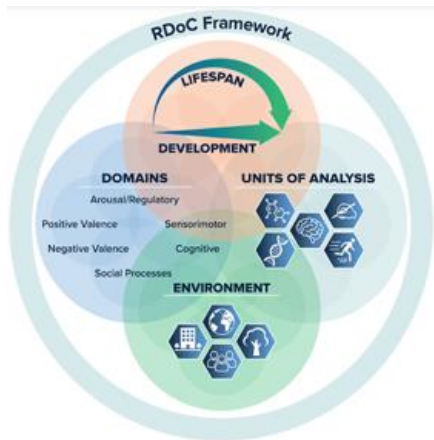
Giorgia Michelini^{1,2}, Christina O Carlisi³, Nicholas R Eaton⁴, Jed T Elison⁵, John D Haltigan⁶, Roman Kotov⁷, Robert F Krueger⁸, Robert D Litzman⁹, James J Li^{10,11}, Holly F Levin-Aspenson¹², Giovanni A Salum^{13,14,15}, Susan C South¹⁶, Kasey Stanton¹⁷, Irwin D Waldman¹⁸, Sylvia Wilson⁵

La psychiatrie de précision (PEPR PROPSY) : hypothèses et outils

Le neurodéveloppement Une dimension transnosographique

Anton Iftimovici¹, Renaud Jardri², Aline Lefebvre³, Jasmina Mallet^{4,5}, Antoine Lefrere^{6,7}

A Neurodevelopmental Perspective on the Research Domain Criteria (RDoC) Framework
 B.J. Casey^{1,2} · Mory Ellen Oltiveri³ · Thomas Insel⁴



2. Preliminary results

Preliminary result



The neurodevelopmental hypothesis as a stratification perspective in Bipolar disorder?

Expert center for Bipolar Disorder

- Early Onset
- Neurodevelopmental trajectory
- Different disorders
- Therapeutic resistance

Preliminary result



1. No consensus on the existence of a neurodevelopmental (ND) phenotype in bipolar disorder
2. Lack of data on prognosis and treatment response
3. Limited clinical implementation



**Defining and validating a
neurodevelopmental phenotype in
bipolar disorder**

Preliminary result

Neurodevelopmental load score in Bipolar Disorder

1. Identify and convert to binary neurodevelopmental items
2. Reduce number of variable
3. Training and test sample
4. Clustering analysis
5. Computation of a Neurodevelopmental load score
6. Stratify according prognosis

Refining Criteria for a Neurodevelopmental Subphenotype of Bipolar Disorders: A FondaMental Advanced Centers of Expertise for Bipolar Disorders Study

Antoine Lefrere, Ophélie Godin, Stéphane Jamain, Yecodji Dansou, Ludovic Samalin, Martin Alda, Bruno Aouizerate, Valérie Aubin, Romain Rey, Martina Contu, Philippe Courtet, Caroline Dubertret, Emmanuel Haffen, Dominique Januel, Marion Leboyer, Pierre-Michel Llorca, Emeline Marlinge, Mirko Manchia, Samantha Neilson, Emilie Olié, Pasquale Paribello, Marco Pinna, Mircea Polosan, Paul Roux, Raymund Schwan, Leonardo Tondo, Michel Walter, Eleni Tzavara, Guillaume Auzias, Christine Deruelle, Bruno Etain, and Raoul Belzeaux

Preliminary result

Neurodevelopmental load score in Bipolar Disorder

1. **Identify and convert to binary neurodevelopmental items**
2. Reduce number of variable
3. Training and test sample
4. Clustering analysis
5. Computation of the Neurodevelopmental load score
6. Stratify according to prognosis

Neurodevelopmental Item
Paternal Age
Maternal age
Family history of psychiatric disorder
Perinatal Infection
Delivery mode
Early onset of BD/SCZ/Dep
Early onset of substance disorder
Early onset of eating disorder onset
Early onset of anxiety disorder
Handedness
Childhood trauma
Psychotic characteristic
ADHD
Learning disabilities

Preliminary result

Neurodevelopmental load score in Bipolar Disorder

1. Identify and convert to binary neurodevelopmental variables
2. **Reduce number of variable**
3. Training and test sample
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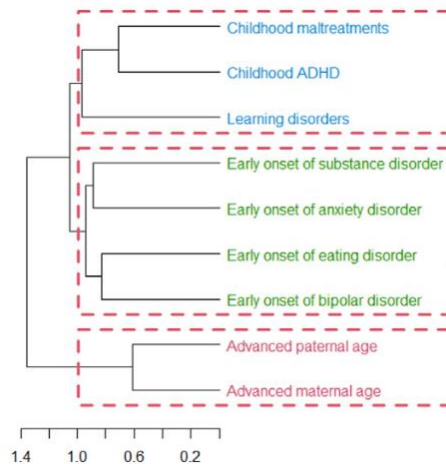
Advanced maternal age
ADHD
Advanced paternal age
Early onset of anxiety disorder
Early onset of bipolar disorder
Childhood trauma
Early onset of eating disorder
Specific learning disorder
Early onset of substance use disorder

Preliminary result

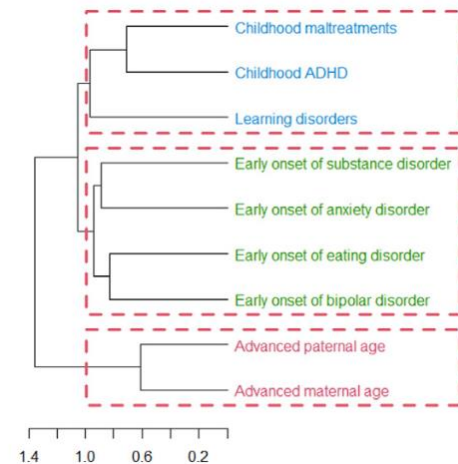
Neurodevelopmental load score in Bipolar Disorder

1. Identify and convert to binary neurodevelopmental variables
2. Reduce number of variable
3. **Training and test sample**
4. **Clustering analysis**
5. Computation of the Neurodevelopmental load score
6. Stratify according to prognosis

Training sample
N = 2495



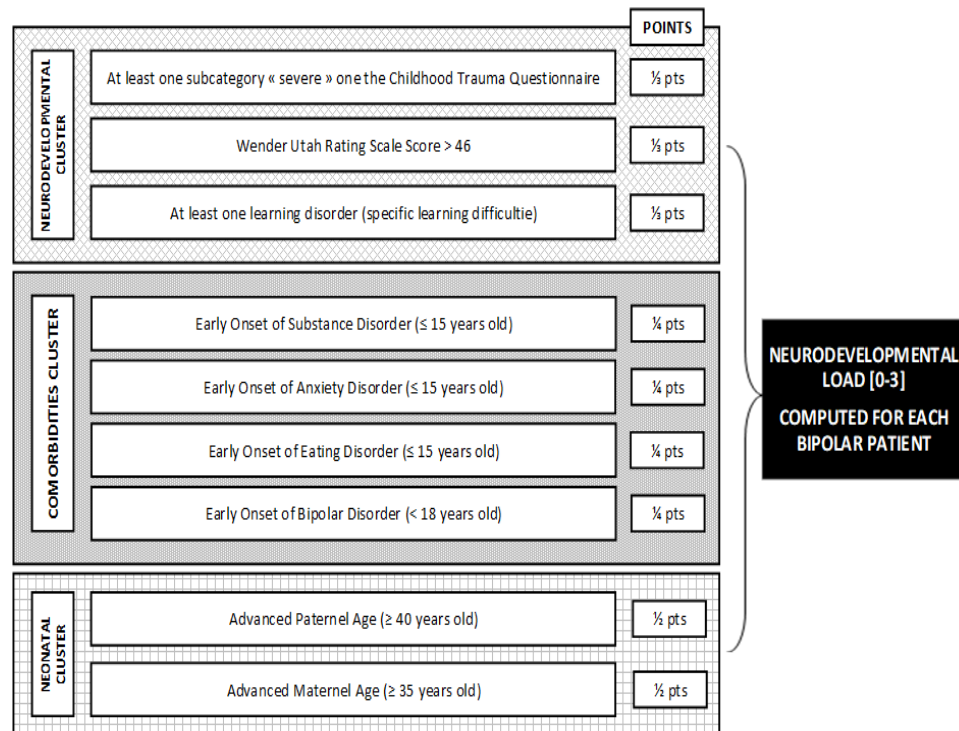
Test sample
N=1329



Preliminary result

Neurodevelopmental load score in Bipolar Disorder

1. Identify ans convert to binary neurodevelopmental variables
2. Reduce number of variable
3. Training and test sample
4. Clustering analysis
5. **Computation of the Neurodevelopmental load score**
6. Stratify according prognosis



Preliminary result

Neurodevelopmental load score in Bipolar Disorder

1. Identify ans convert to binary neurodevelopmental variables
2. Reduce number of variable
3. Training and test sample
4. Clustering analysis
5. Computation of the Neurodevelopmental load score
6. **Stratify according prognosis**

Prognosis

Suicide attempt (p<0.001)
n episodes total (p<0.001)
n Depressive episode (p<0.001)
n mixed episodes (p<0.001)
Functioning (p<0.001)
Rapid cycle(p<0.001)

Lithium response

ALDA $\beta = -1.74$, 95% CI [-3.14 to -0.32] p = 0.016

Neurological soft sign

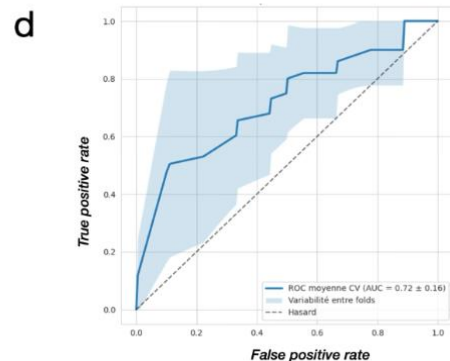
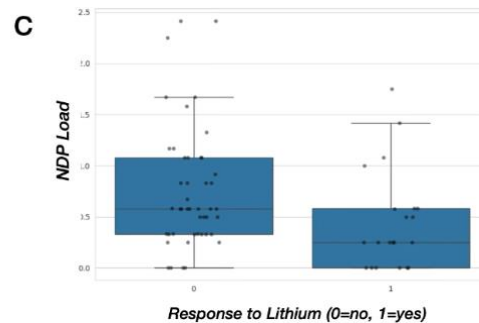
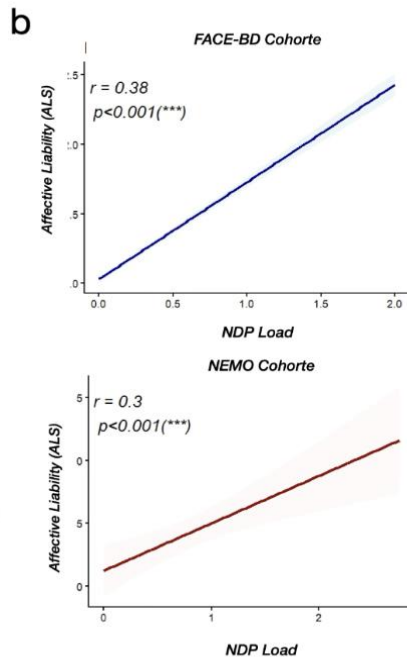
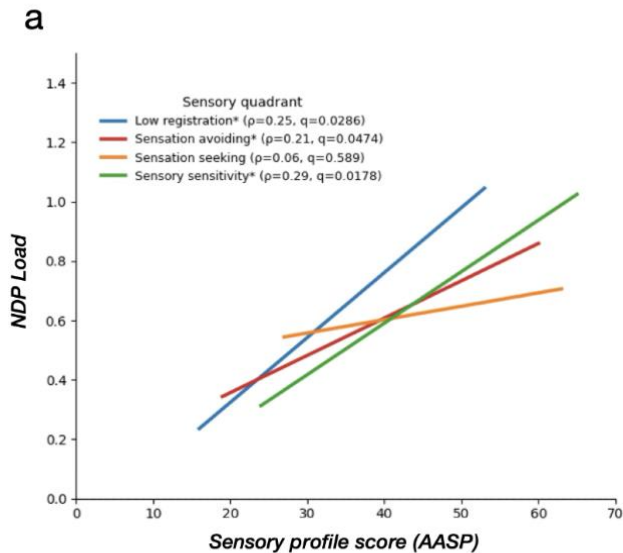
NSS $\beta = 1.01$; 95% CI [0.18 to 1.56], p = 0.014

Polygenic Risk Score

PGS-TDAH
F= 8,98;p=0.004

Preliminary result

New variable of interest



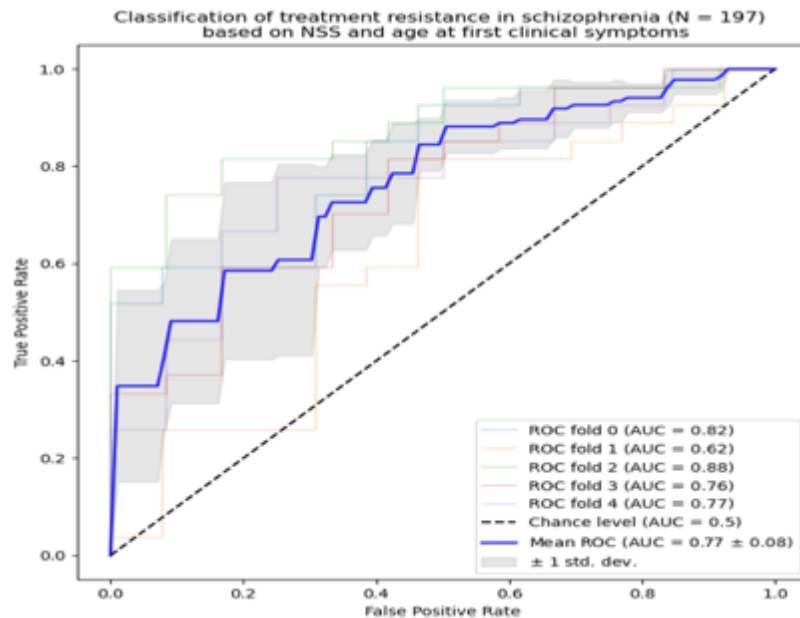
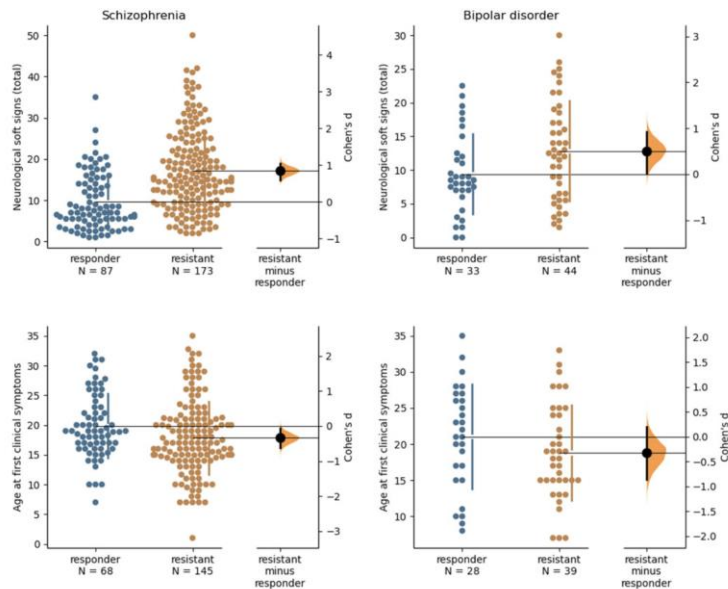
Sensory processing

EMOTIONAL
dysregulation

Lithium response

Preliminary result

Neurological soft sign as neurodevelopmental predictors of resistance in Bipolar disorder and schizophrenia



Preliminary result

Morphometric MRI as neurodevelopmental biomarker

Sulcation

Morphometric marker of neurodevelopment

Sulcal pits

- Emergence points
- Cortical folding

Régis et al., 2005, Mangin et al., 2004

Neurodevelopmental disorders

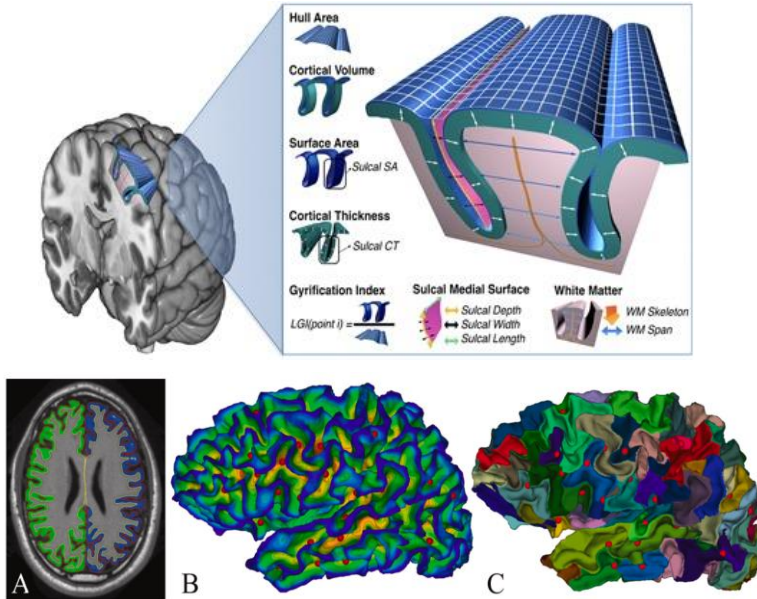
Intellectual disability *Im K et al 2014*

Autism. *Brun et al 2016*

Polymicrogyric *Im K 2014*

ADHD *Li et al 2020*

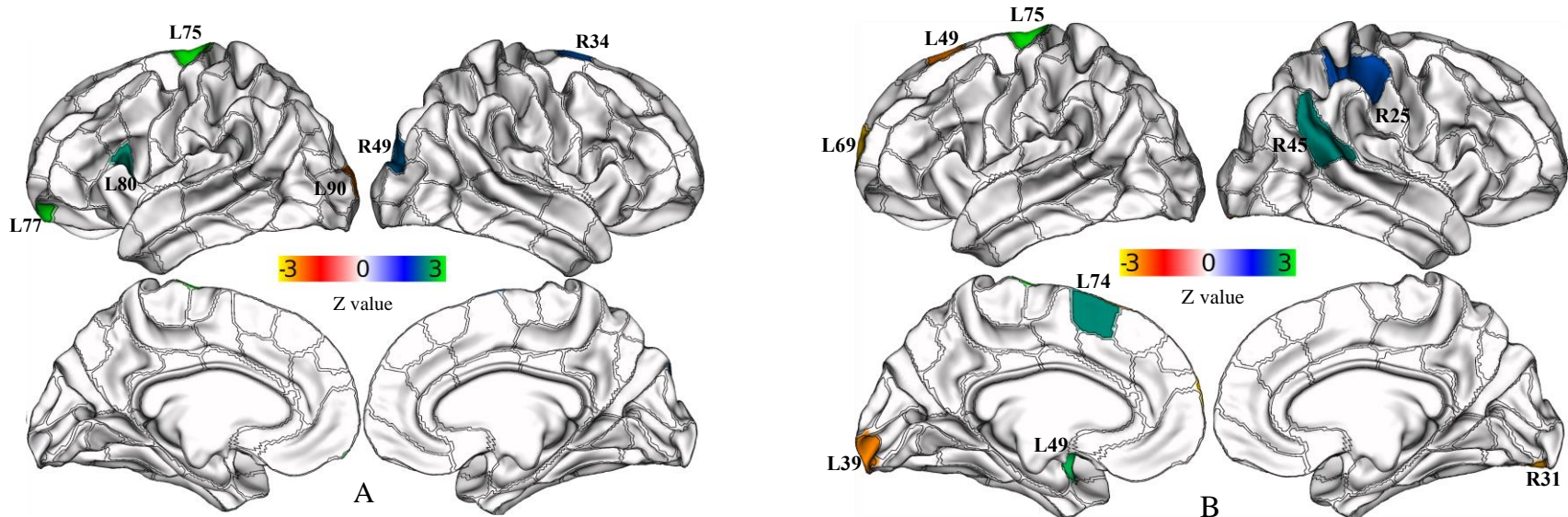
Bipolar disorder *Lefrere et al 2025*



Preliminary result

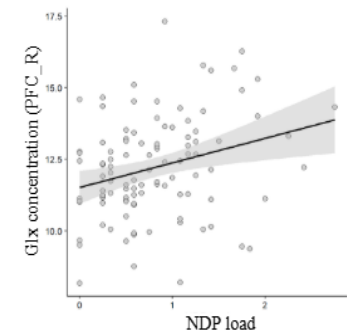
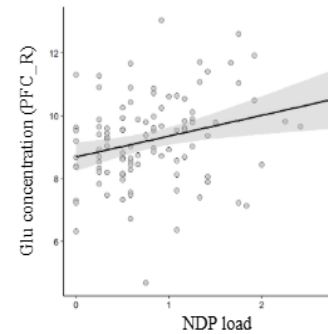
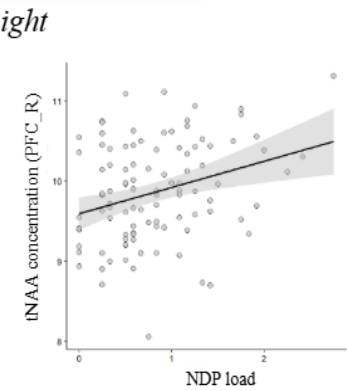
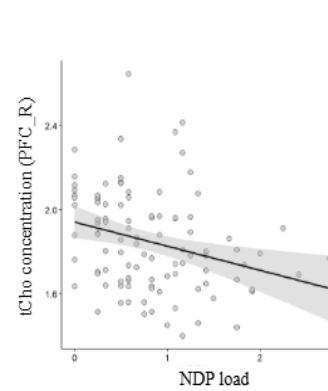
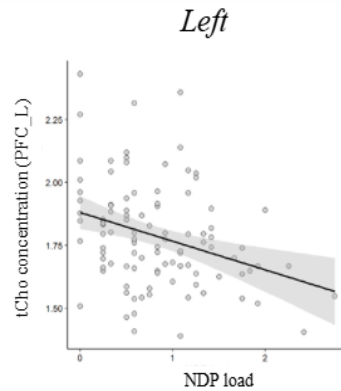
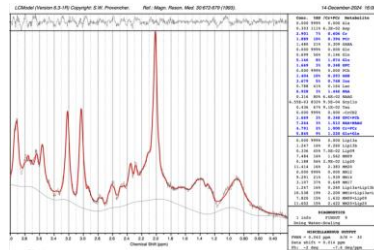
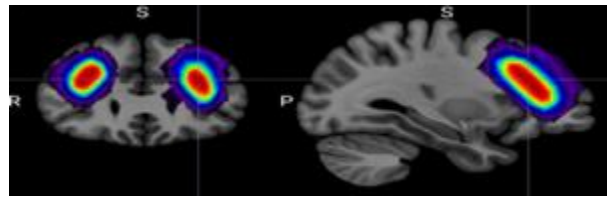
Morphometric MRI as neurodevelopmental biomarker

- Global analysis: Higher frequency of sulcal pits in BD-ND compared with BD ($Z = 2.01$, $p = 0.04$)
- Local analysis: Higher occurrence of sulcal pits in BD-ND compared with BD ($Z = 4.6$, $p\text{FDR} = 0.00026$)



Preliminary result

MRI Spectroscopy: a tool for pathophysiological understanding?



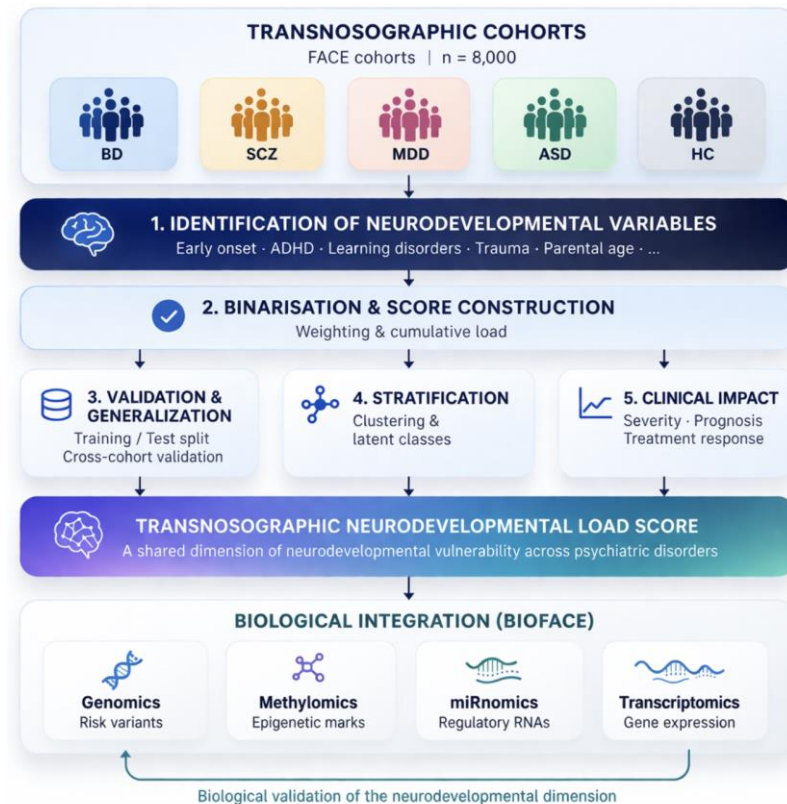
Disorder	Results
Schizophrenia	<ul style="list-style-type: none"> tNAA levels tCho/Cr ratio levels
Autism Spectrum Disorder	<ul style="list-style-type: none"> tNAA levels GABA levels tCho levels
Extremely Preterm newborn	<ul style="list-style-type: none"> tCho/Cr ratio levels tNAA/Cr ratio levels
ADHD/Dyslexia	<ul style="list-style-type: none"> tCho levels tCho levels

3. FACE (FondaMental Advanced center of expertise) cohorts: FUTURE ANALYSIS

Ongoing work

Transnosographic neurodevelopmental load score

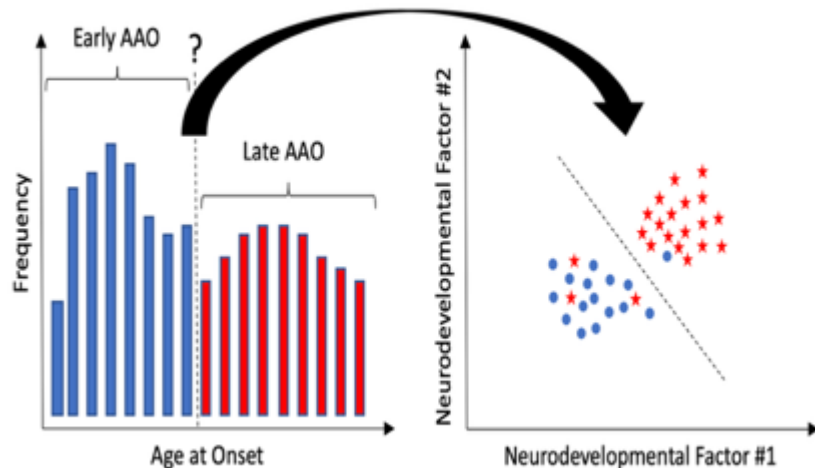
1. Identify and convert to binary neurodevelopmental items
2. Define age of onset or parental age
3. Computation of a transnosographic neurodevelopmental score load
4. Sensibility analysis by disorder
5. Stratify according to prognosis
6. Identify gene of interest and PGS (BioFACE)



Ongoing work

Transnographic neurodevelopmental load score

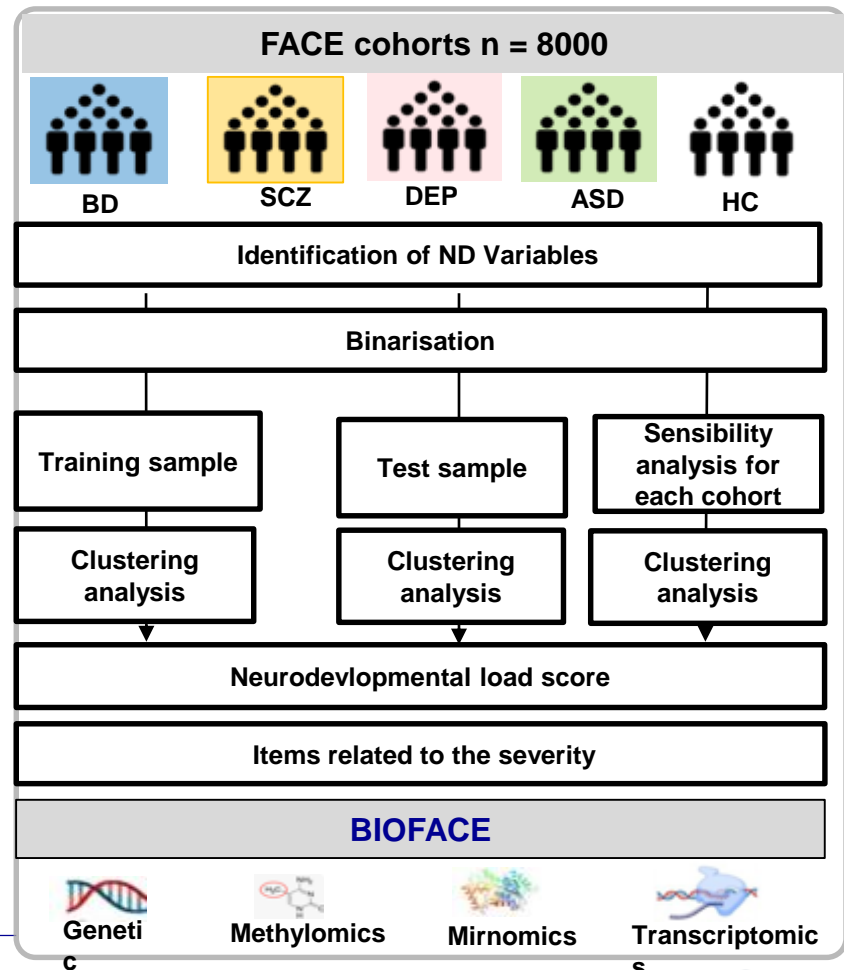
1. Identify and convert to binary neurodevelopmental items
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Corponi F, Lefrere A, Leboyer M, Bellivier F, Godin O, Loftus J, et al. Definition of early age at onset in bipolar disorder according to distinctive neurodevelopmental pathways: insights from the FACE-BD study. **Psychol Med.** 28 fevr 2023;1-9.

Ongoing work

1. Identify and convert to binary neurodevelopmental items
2. Define age of onset or parental age
3. **Computation of transnosographic neurodevelopmental score load**
4. **Sensibility analysis by disorder**
5. **Stratify according to prognosis**
6. **Identify gene of interest and PGS (BioFACE)**



3. Frenchmind cohort: roadmap

What we plan to do ?

Data of interest

Neurodevelopmental checklist

- Age parents
- Toxic
- Perinatal infection
- Prematurity
- Birth Weight
- PC
- Childbirth
- Puberty
- Trauma
- Toxic
- DSM
- Studies
- Grade repetition
- ATCD neurodev
- Psychomotor Follow-up
- Speech therapy follow-up
- First impact
- First Episode
- First treatment

Cognition

- **CANTAB**
SOC, Digit span, ERT
- **TOM test:**
RMET and Frith-Happé
- **WAIS IV**
similarities, matrices, codes
- **CVLT**
Verbal Learning and Memory Test
- **Saint Hilaire's Verbal Fluency**
-
- **Sensoriality**
- Glasgow

Neurological soft sign



Biomarkers

MRI:

- Anatomical
- Resting-state
- Functional

EEG

- Frequency
- Topographical
- Quantitative

Genetics:

SNV, CNV, SNP, PGS

Biology:

- Transcriptomic
- Metabolomic

What we plan to do ?

**French Mind
(n = 3,000)**
Large-scale cohort
Replication
External validation
Normative modeling

Refinement of neurodevelopmental score
Neurological soft signs (NSS)
Neurodevelopmental checklist
Sensory processing

Multimodal data integration

MRI (structural / diffusion / resting-state)
EEG
Metabolomics
Digital phenotyping

Outcomes
Stratification
Prediction
Multimodal signatures
New treatment strategies
Clinical decision support tools



PROGRAMME
DE RECHERCHE
INTERNATIONALE
DE PRECISION

French Minds : International partnership

Name	Affiliation	Country	Occupation	Publications	Contact
Giorgia Michelini	King's college Queen Mary	England	Associate professor	Michelini G, et al . Where do neurodevelopmental conditions fit in transdiagnostic psychiatric frameworks? Incorporating a new neurodevelopmental spectrum. World Psychiatry. 2024 Oct;23(3):333-357. doi: 10.1002/wps.21225. PMID: 39279404; PMCID: PMC11403200.	g.michelini@qmul.ac.uk
Marin Jukic	Karolinska institute	Sweden	Senior researcher	Iftimovici A, Krebs E, Dalfin W, Legrand A, Scoriels L, Martinez G, Bendjema N, Duchesnay E, Chaumette B, Krebs MO. Neurodevelopmental predictors of treatment response in schizophrenia and bipolar disorder. Psychol Med. 2024 Oct 15;54(13):1-12. doi: 10.1017/S0033291724001776. Epub ahead of print. PMID: 39402801; PMCID: PMC11536111.	marin.jukic@ki.se
Smeland	Center for precision Psychiatry	Norway	Professor	Smeland OB, Busch C, Andreassen OA, Manchia M. Novel Multimodal Precision Medicine Approaches and the Relevance of Developmental Trajectories in Bipolar Disorder. Biol Psychiatry. 2025 Aug 15;98(4):343-353. doi: 10.1016/j.biopsych.2025.03.010. Epub 2025 Mar 27.	ole.andreassen@medisin.uio.no
Mirko Manchia	University of Cagliari	Italy	Associate Professor	Smeland OB, Busch C, Andreassen OA, Manchia M. Novel Multimodal Precision Medicine Approaches and the Relevance of Developmental Trajectories in Bipolar Disorder. Biol Psychiatry. 2025 Aug 15;98(4):343-353. doi:	mirkomanchia@unica.it
C Piquet	University of	Switzerland	MD PhD	Pindi P, Houenou J, Piquet C, Favre P. Real-time	