Aix Marseille Université

institut de neurosciences de la timone

Master's research project

Neurodevelopmental Phenotype of Bipolar Disorder, a Spectroscopy MRI study

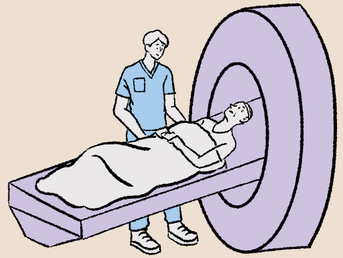
Supervised by **Antoine Lefrère and Christine Deruelle,**

Collaboration with **Julien Sein**

Presented by **Léane Petitgas**

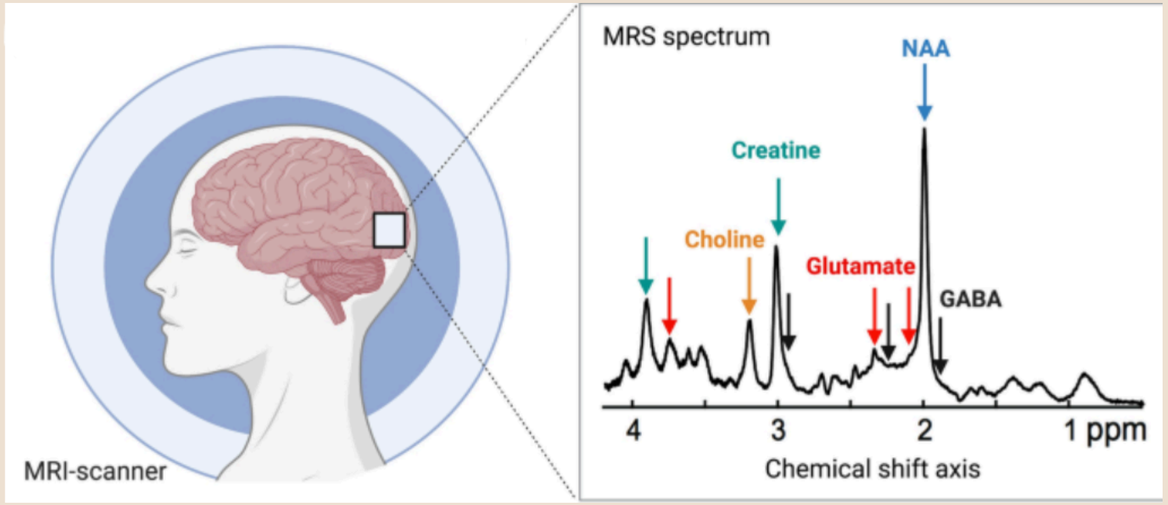
CanoP | 2025

Introduction



H- Magnetic Resonance Spectroscopy (MRS)

- Analyses the **chemical composition** using hydrogen nuclei signals
- Generates spectra that represent **metabolite level**
- Each peak = one metabolite
- Quantification via peak integration or curve-fitting
- Referenced to an **internal reference** or external phantom.



Metabolites	Position (ppm)	Role
Lactate (Lac)	1.3 ppm	Anaerobic metabolism
N-AcetylAspartate (NAA)	2.0 ppm	Neuronal integrity
Glutamate (Glu)/ Glutamine (Gln) / Glx / GABA	2.1–2.5 ppm	Excitatory and inhibitory neurotransmission
Aspartate (Asp)	2.8 ppm	Cellular energy metabolism, Excitatory neurotransmission
Creatine (Cr)	3.0 ppm	Energy metabolism marker
Choline (Cho)	3.2 ppm	Membrane turnover and cellular density
Taurine (Tau)	3.4 ppm	Amino acid derivative and neurotransmitter
Myo-Inositol (m-Ins)	3.5 ppm	Glial function and osmoregulation

Literature Review

Bipolar disorder :

Chabert et.al (2022) : meta-analysis of MRS (N= 873 BD, N=800 controls).

1

- **Alteration in tNAA levels** in depressive and remitted patients ⟶ impairments in neuronal plasticity
- **Gln levels** in remitted patients (only in the ACC) ⟶ due to the euthymic periods

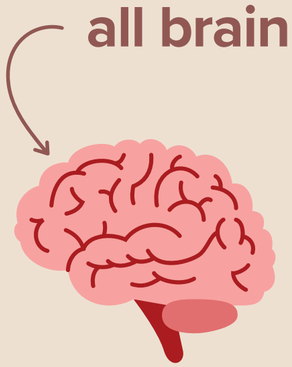
Tannous et.al (2021) : children and adolescents (N=24 BD, N=25 controls).

2

- **tNAA levels** ⟶ either neuronal alterations or mitochondrial dysfunction.
- **tCho levels** ⟶ phospholipid metabolism dysregulation, essential for cell membrane integrity.

Literature Review

Neurodevelopmental disorders :



Disorder	Results
Schizophrenia	• ↘ tNAA levels • ↘ tCho/Cr ratio levels
Autism Spectrum Disorder	• ↘ tNAA levels • ↘ GABA levels • ↘ Glu levels • ↘ tCho levels
Extremely Preterm newborn	• ↘ tCho/Cr ratio levels • ↘ tNAA/Cr ratio levels
ADHD/Dyslexia	• ↘ tCho levels

Derbyshire et.al (2023)

Cheong et.al (2016)

Objective

Characterize the **neurodevelopmental phenotype** in BD using **MRS**, aiming to identify biomarkers through metabolite analysis.

Hypothesis

Neurodevelopmental load

- **t N-AcetylAspartate (tNAA) levels**
  = marker of greater severity

- **Glutamatergic levels**
  = marker of greater severity

Chabert et.al (2022)

- **tCholine (tCho) levels**
  = marker of neurodevelopment

Tannous et.al (2021)

Methodology

NEMO Cohort:

Recruited at the Bipolar Expert Centre, Sainte-Marguerite Hospital.

Population of 120 bipolar patients, no control.

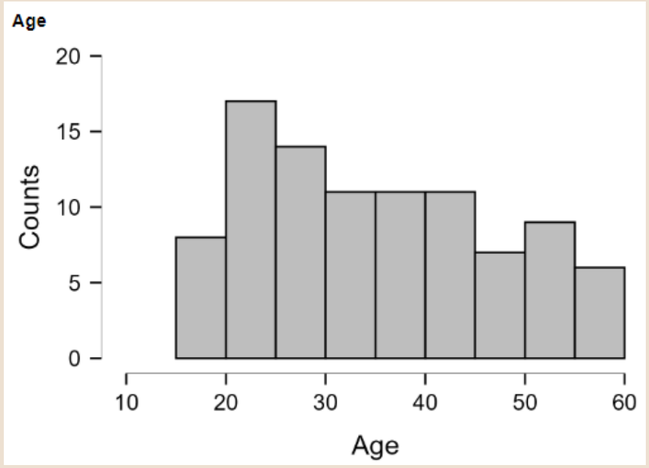
Bipolar patient
***N* = 120**

↓

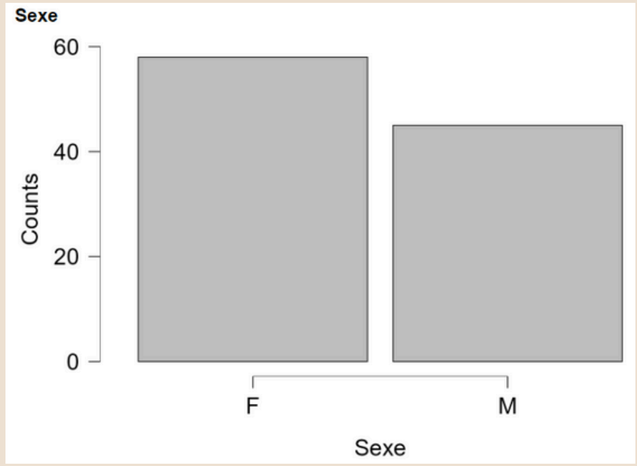
MRI data
***N* = 108**

↓

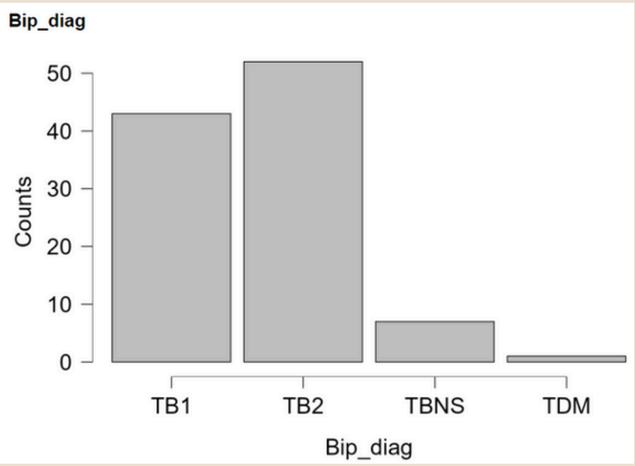
Control quality
***N* = 103**



Median age at 35 years old (18-59)



58 women // 45 men



43 BD-I // 52 BD-II

Methodology

NEMO Cohort:

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Inclusion Criteria
• Aged 18 to 60 years, • Have received a diagnosis of BD-I, BD-II or BD not otherwise specified, according to the diagnostic criteria of the DSM-V.

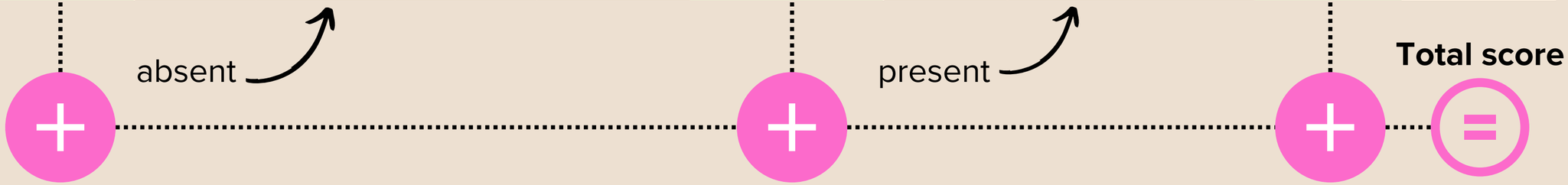
Exclusion Criteria
• Presence of symptomatic or unstable physiological or medical conditions, • Comorbid ASD or SCZ, • History of severe head trauma, • Comorbid neurological disorder, • Moderate to severe substance use disorders, • Being under guardianship, • Inability to provide informed consent, • Insufficient command of the French language.

Methodology

NDP load measurement :

Continously :

Age_mere_birth	Age_Pere_birth	Score_Cluster_ Neonat	Bip<18ans	Tanx <16ans	TCA<16ans	TLU<16ans	Score_Cluster_Early Onset	Trauma_CTQ	TDAH_WURS	Tb_dys	Score_Cluster_ Dvlpmt	NDP_load
0	0	0	1	1	1	0	0.75	1	1	0	0.67	**1.42**
0	0	0	0	0	1	0	0.25	1	1	0	0.67	**0.92**



Methodology

NDP load measurement :

Continously :

Age_mere_birth	Age_Pere_birth	Score_Cluster_Neonat	Bip<18ans	Tanx <16ans	TCA<16ans	TLU<16ans	Score_Cluster_Early Onset	Trauma_CTQ	TDAH_WURS	Tb_dys	Score_Cluster_Dvlpmt	NDP_load
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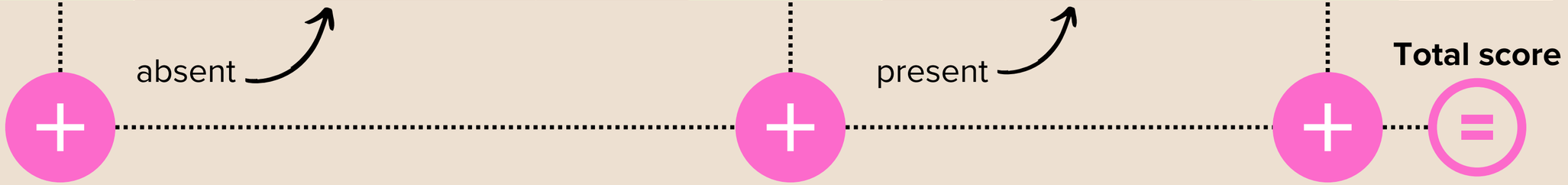
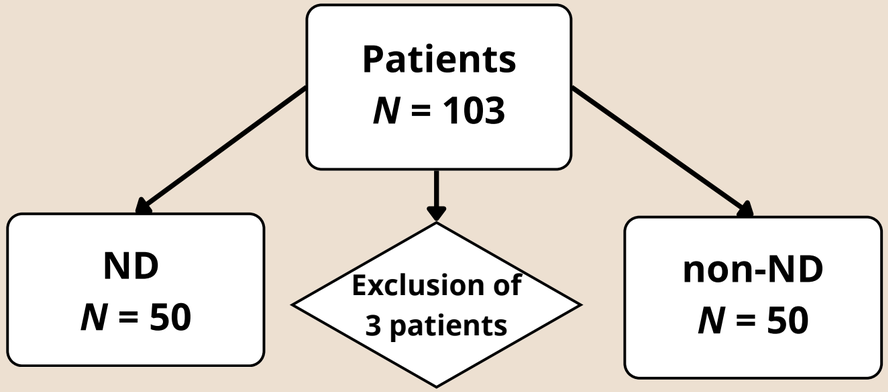
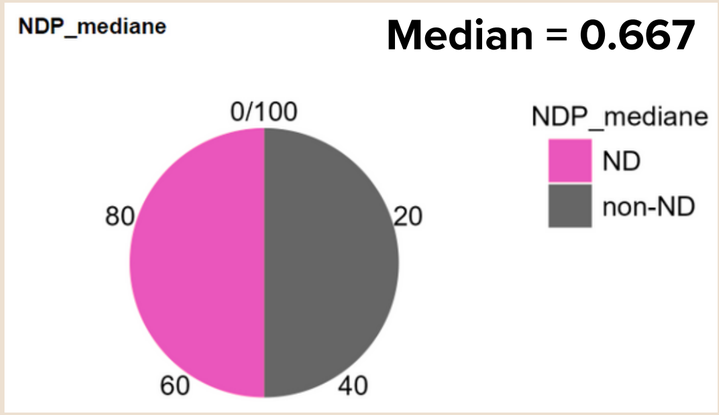
0	0	0	0	0	1	0	0.25	1	1	0	0.67	0.92



By group :

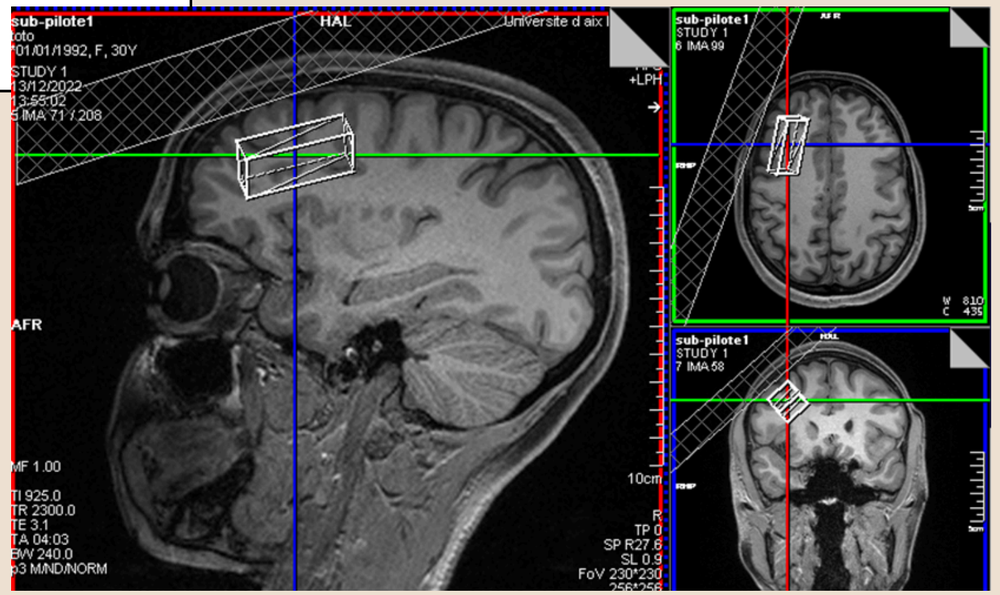




Methodology

Imaging

- 3.0 T Siemens MRI
- SVS (Single Voxel Spectroscopy)
- PRESS sequence (Point RESolved Spectroscopy)
- **Right and Left PreFrontal Cortex** (40 x 10 x 20 mm3)
- Saturation band on the bone



Collaboration with **Julien Sein, CERIMED**

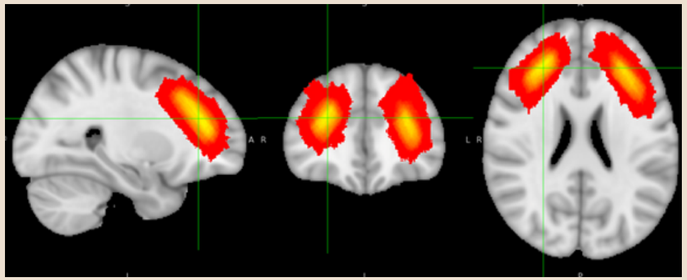
Methodology

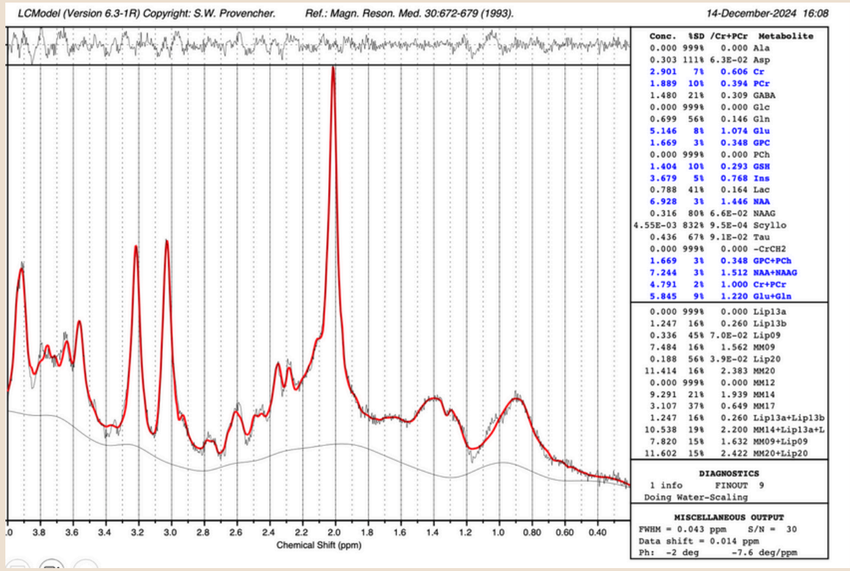
Data analysis

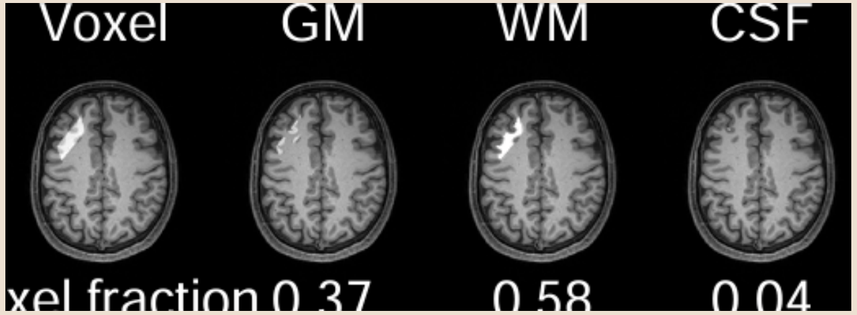
- **LCModel** software (water as reference)
- Correction of different tissues (GM, WM, CSF)

Quality control

- Spectra control + voxel placement :
103 patients
- Metabolite fitting :
Gln, Glu, Glx, mIns, tNAA, tCho and tCr







Provencher S. W. (2001)

Methodology

Sensibility Analysis

LCModel software :

- Most used in MRS,
- Reliability and reproducibility
- Quality control metrics

Osprey Software :

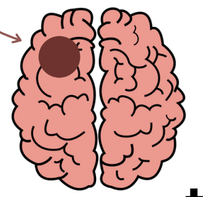
- More recent,
- Tissue segmentation,
- Quality control metrics,
- Simplified data handling but

Clermont Ferrand basis set

MRSCloud basis set

Results

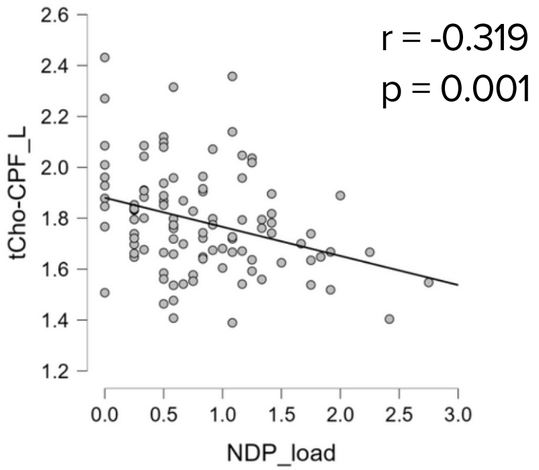
Left PFC



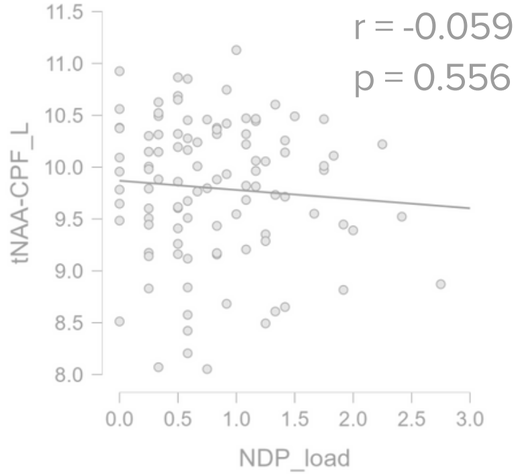
Relationship between **NDP load** and metabolite level

Continously :

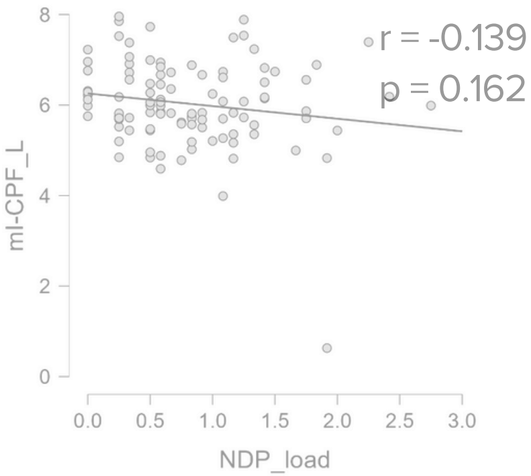
tCho



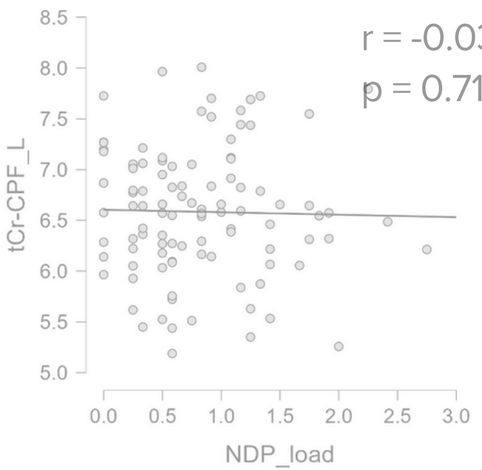
tNAA



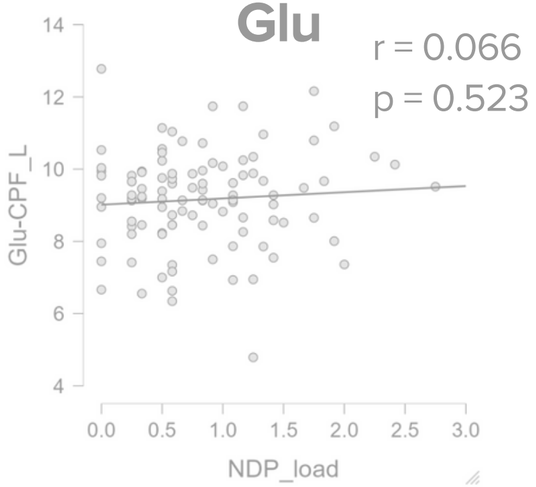
mI



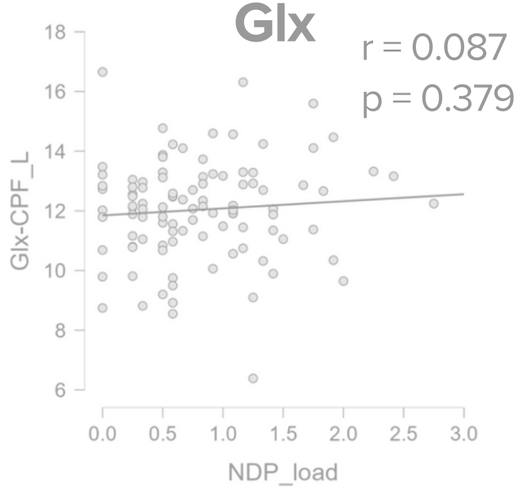
tCr



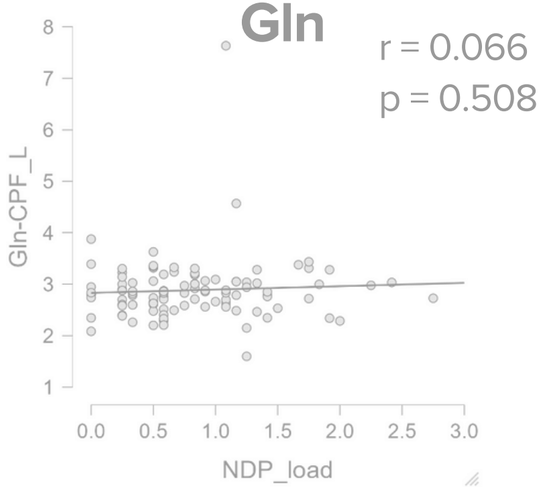
Glu



Glx



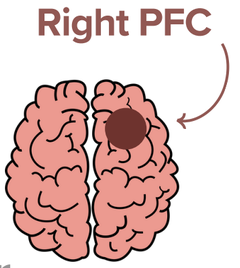
Gln



Results

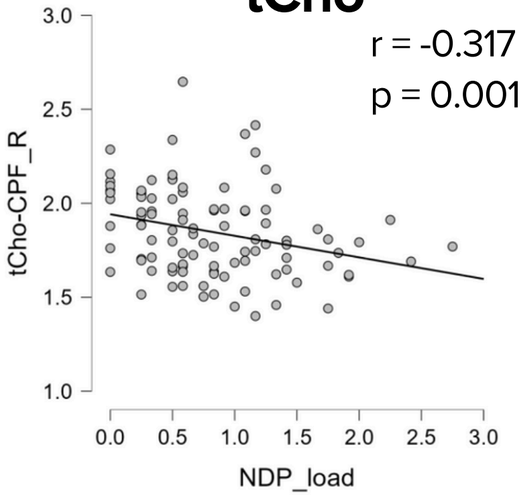
Relationship between **NDP load** and metabolite level

Continously :



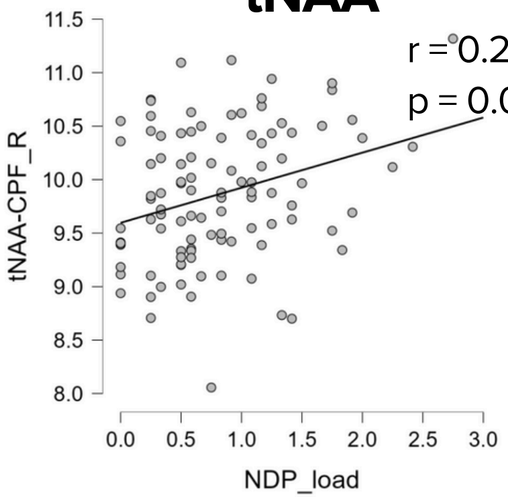
tCho

r = -0.317
p = 0.001



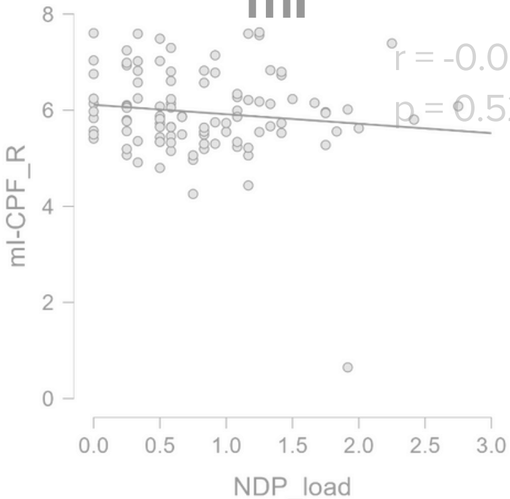
tNAA

r = 0.271
p = 0.006



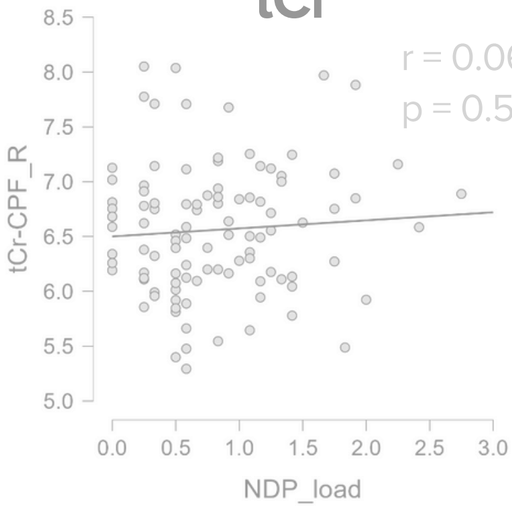
mI

r = -0.063
p = 0.524



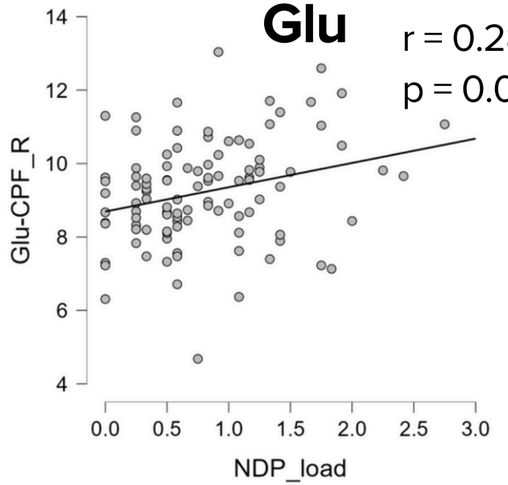
tCr

r = 0.063
p = 0.529



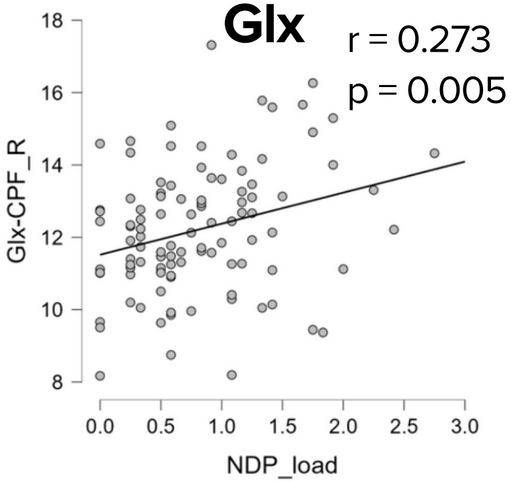
Glu

r = 0.280
p = 0.004



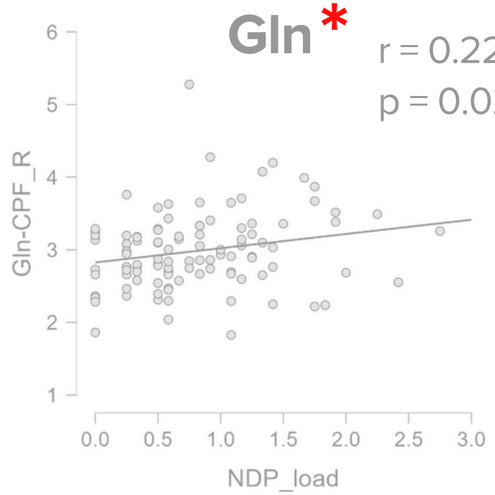
Glx

r = 0.273
p = 0.005



Gln*

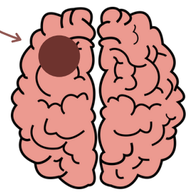
r = 0.227
p = 0.021



*cofactors correction

Results

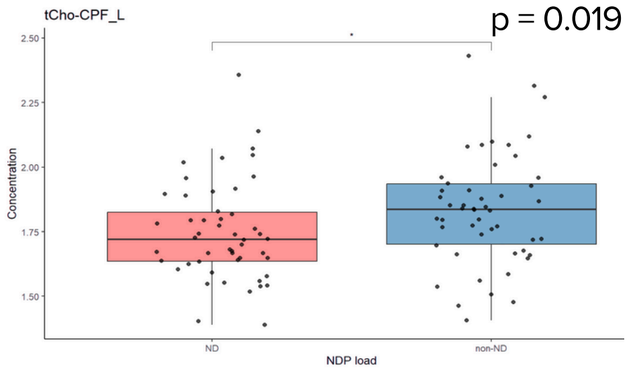
Left PFC



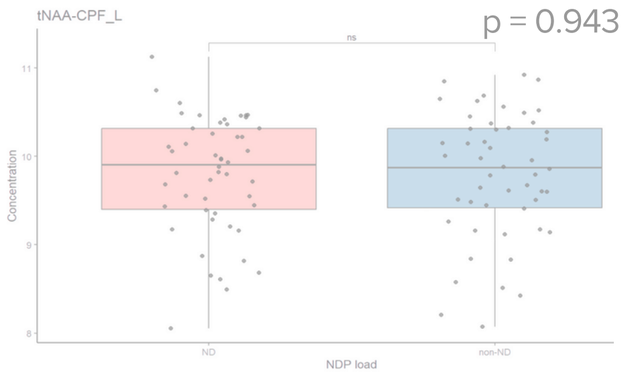
Relationship between **NDP load** and metabolite level

By group:

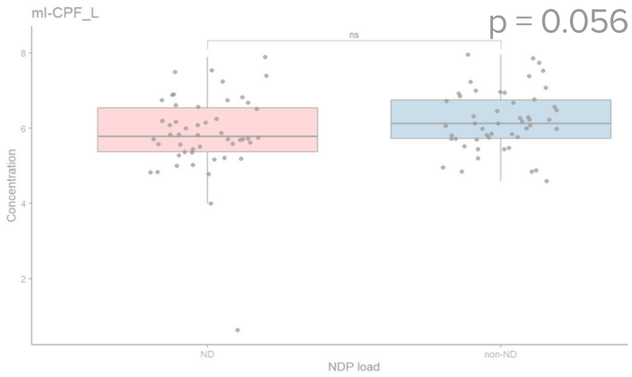
tCho



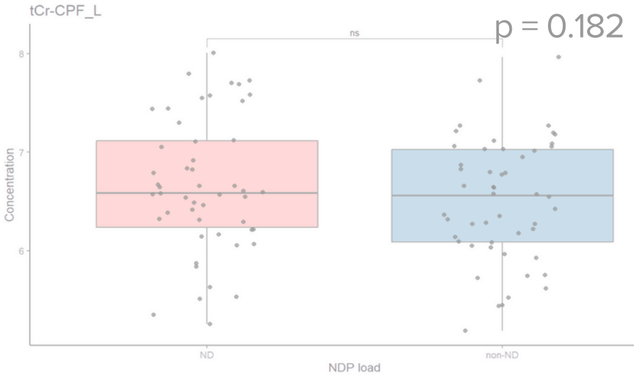
tNAA



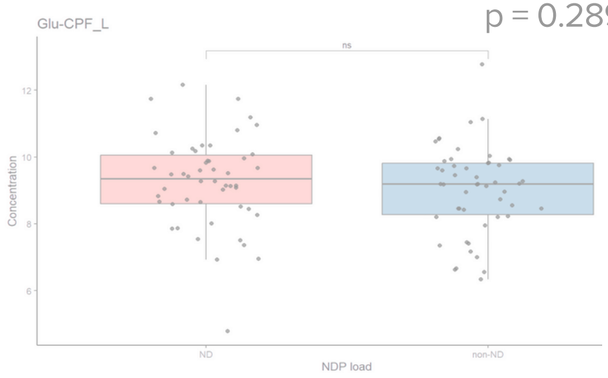
mI



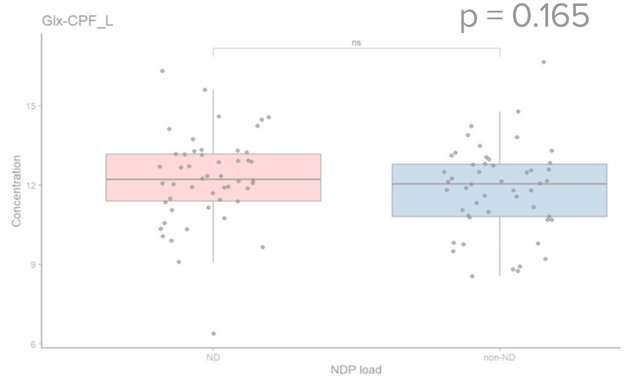
tCr



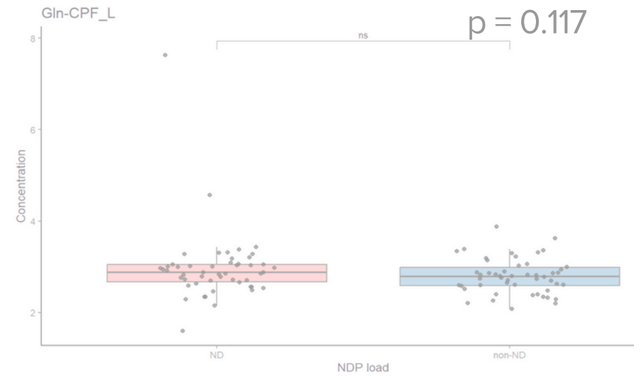
Glu



Glx



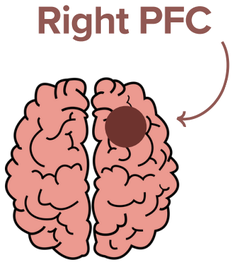
Gln



Results

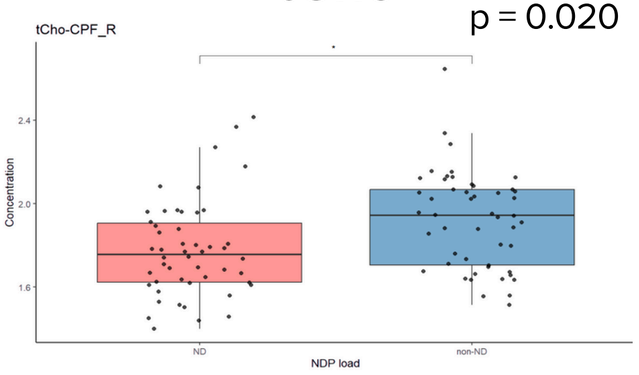
Relationship between **NDP load** and metabolite level

By group:



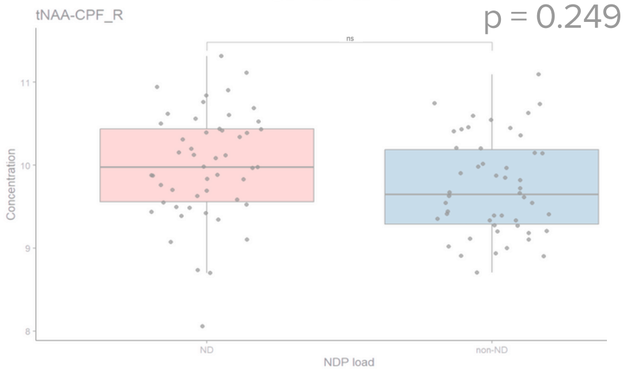
tCho

p = 0.020



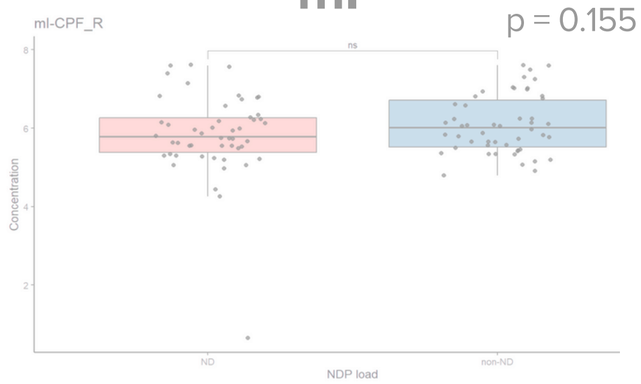
tNAA*

p = 0.249



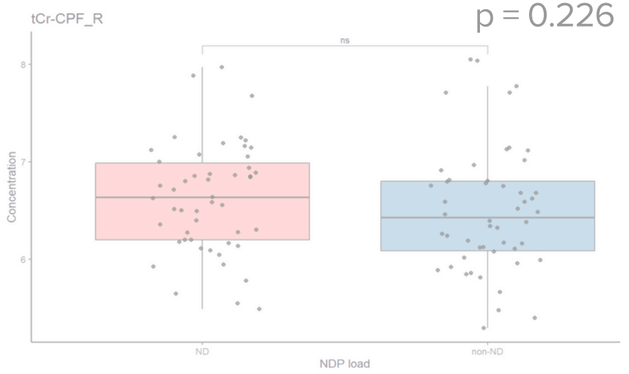
mI

p = 0.155



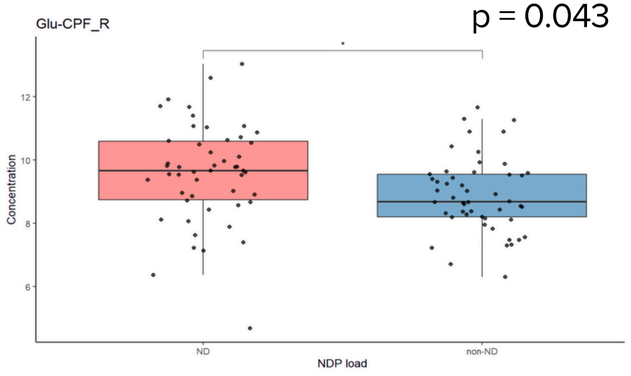
tCr

p = 0.226



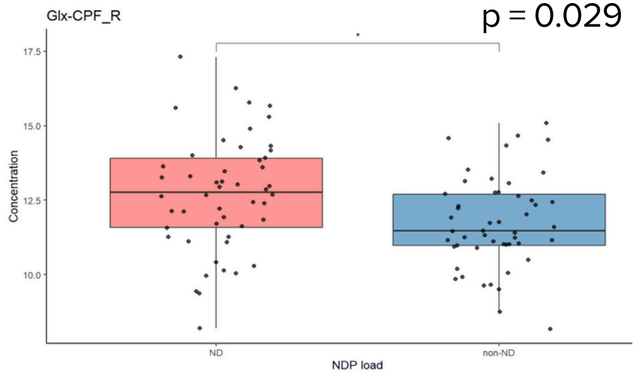
Glu

p = 0.043



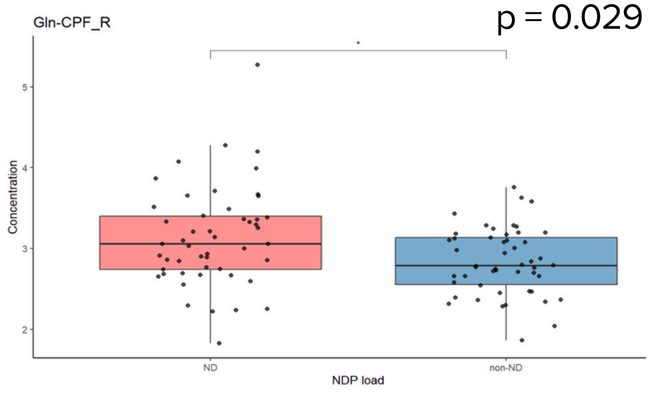
Glx

p = 0.029



Gln

p = 0.029



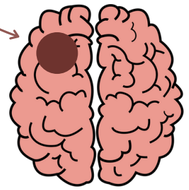
*cofactors correction

Results

Relationship between **NDP load** and metabolite level

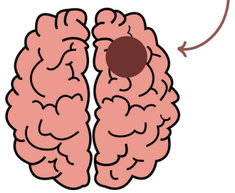
LCModel - Clermont Ferrand

Left PFC



- tCho ⊖

Right PFC



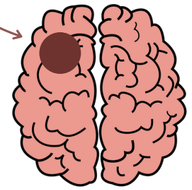
- Glu ⊕
- Glx ⊕
- tNAA ⊕
- tCho ⊖

Results

Relationship between **NDP load** and metabolite level

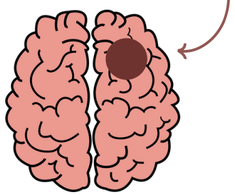
LCModel - Clermont Ferrand

Left PFC



- tCho ⊖

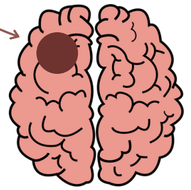
Right PFC



- Glu ⊕
- Glx ⊕
- tNAA ⊕
- tCho ⊖

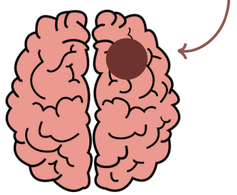
Osprey

Left PFC



- tCho ⊖

Right PFC



- tCho ⊖

Discussion

🧠 Neurodevelopmental load :

- ↗ **NDP load**, ↘ **tCho levels in the bilateral PFC**
- tCho in MRS : indirect marker of **membrane integrity, cellular turnover, and neuroplasticity.**
- ↘ **tCho** ↪ **disruption in membrane metabolism and plasticity.**
- Also found in pediatric BD AND in **neurodevelopmental disorders (ASD, ADHD, Scz).**
- ↗ **tCho levels** in premature newborns ↪ **better IQ, verbal functions, memory**

Cheong et.al (2016)

Discussion

🧠 Neurodevelopmental load :

- ↗ **NDP load**, ↗ **tNAA, Glu, Gln and Glx levels in the right PFC**

- Glu, Gln, Glx: reflection of excitatory neurotransmission.
- tNAA: marker of neuronal integrity and metabolism.

- ↗ **Glu/Gln/Glx + tNAA** ↪ increased neuronal metabolism AND excitatory hyperactivity

- Difference in tNAA (continous) and Gln (categorical) → cofactors correction.

- Also found in **BD and neurodevelopmental disorders** (ASD, ADHD, Scz)

Discussion

Strengths

Classical categorisation of BD

- BD-I, BD-II ⟶ no associated metabolites
- NDP stratification = better biological relevance

NDP analytical approach

- Stable results with **continuous** // **categorical approach**

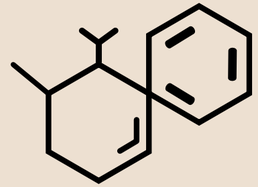
Sensibility analysis

- Analysis confirmed with 3 different MRS software

Limits

- **Caution in Glu/Gln/Glx and tNAA interpretation** (located only in the right PFC + not confirmed with Osprey)
- **No control group**
- **Not all metabolite**

Conclusion



- ↘ **tCho levels** in bipolar patients with a **neurodevelopmental phenotype.**

  ↪ **Biomarker of the neurodevelopmental phenotype**

- **Glutamatergic and tNAA anomalies** are promising but **require confirmation.**

- **Identify earlier and better target interventions for BD with neurodevelopmental forms.**

- Validating the **NDP score** as a **clinical stratification tool**
- **Preclinical models**
- Investigate the relationship between tCho levels, **structural connectivity and cognitive metrics**

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Thank You

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