Toward Precision Psychiatry:
Advancing Neuroimaging Biomarkers Discovery and Personalized Interventions for Mood Disorders

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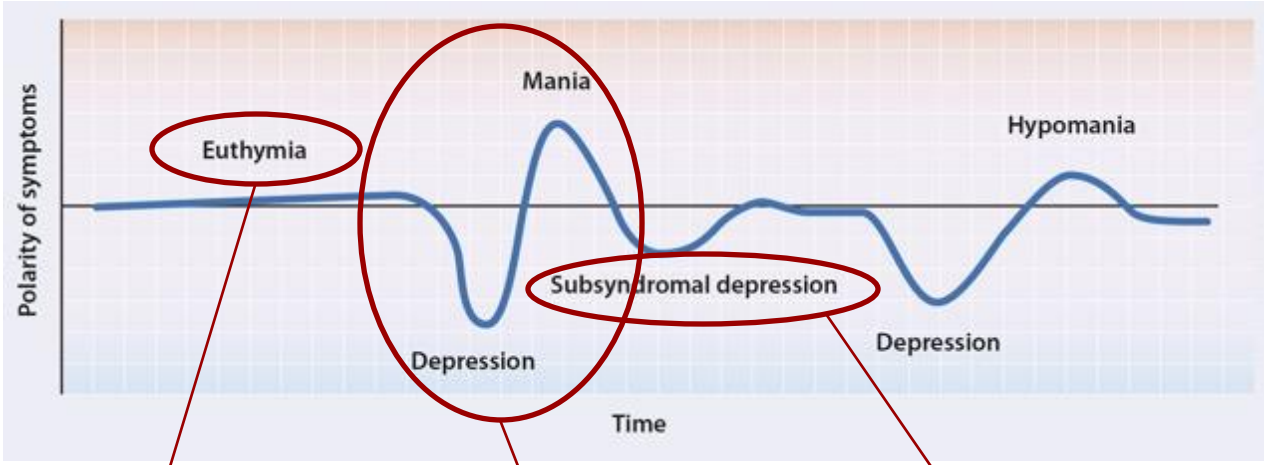
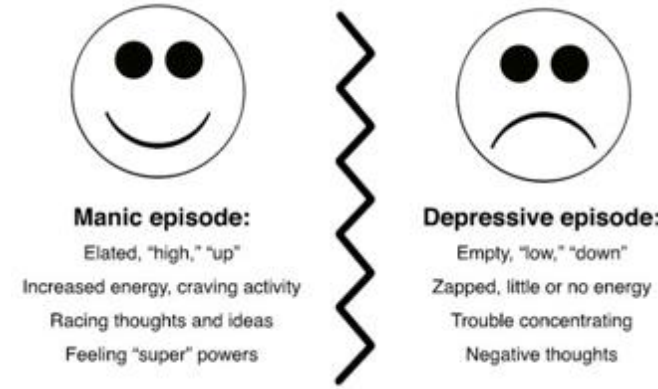
Bipolar Disorder
= severe and chronic mood disease





"*Traits*" characteristics

"*States*" characteristics

Therapeutic options?

- 1% of the general population
- Very high medico-social cost (~7500€ / patient / an)
- Late diagnosis (~10 years)
- Heterogeneity
- Significant functional and socio-professional disabilities

Research questions

- Can neuroimaging helps to better **understand** and diagnose bipolar disorder?

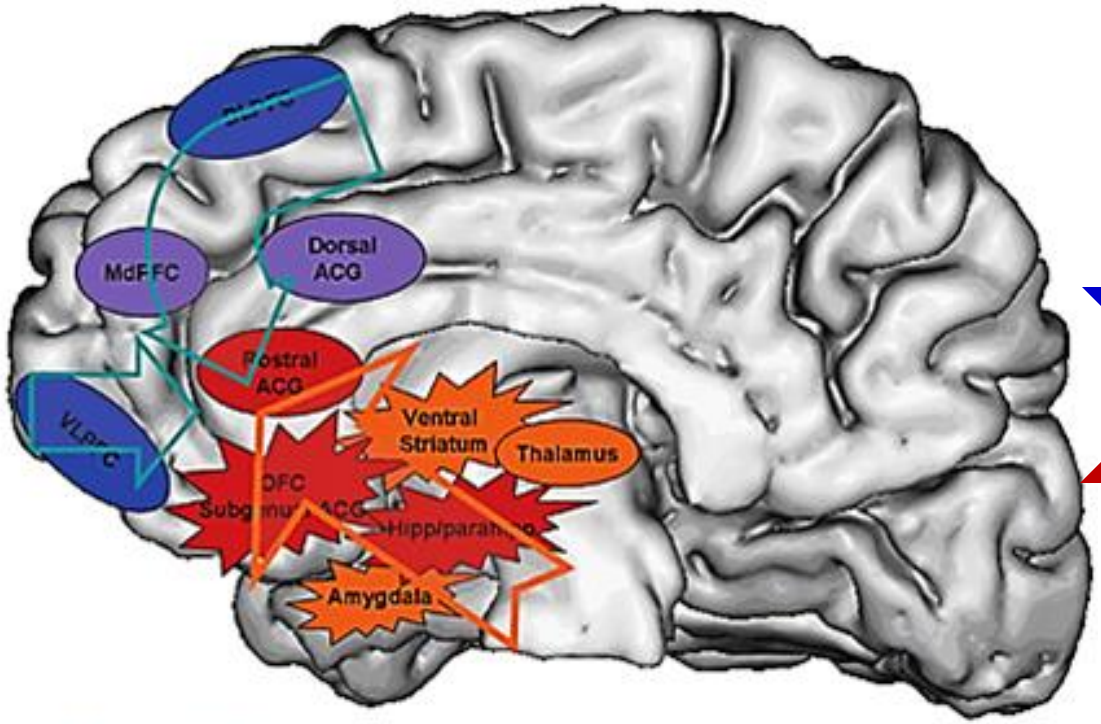
- Can we use machine learning with MRI features to better **diagnose** bipolar disorder?

- Can we use neuroimaging discoveries to **manage** symptoms of mood disorder?

Neuroimaging-based Biomarkers of Bipolar Disorder

Can neuroimaging helps to better understand and diagnose bipolar disorder?

Neurobiological model of BD



DORSAL SYSTEM:

Lateral prefrontal areas (ventral & dorsal)

→ Cognitive control

VENTRAL SYSTEM:

Sub-cortical & limbic + orbito-frontal cortex

→ Emotions perception & génération

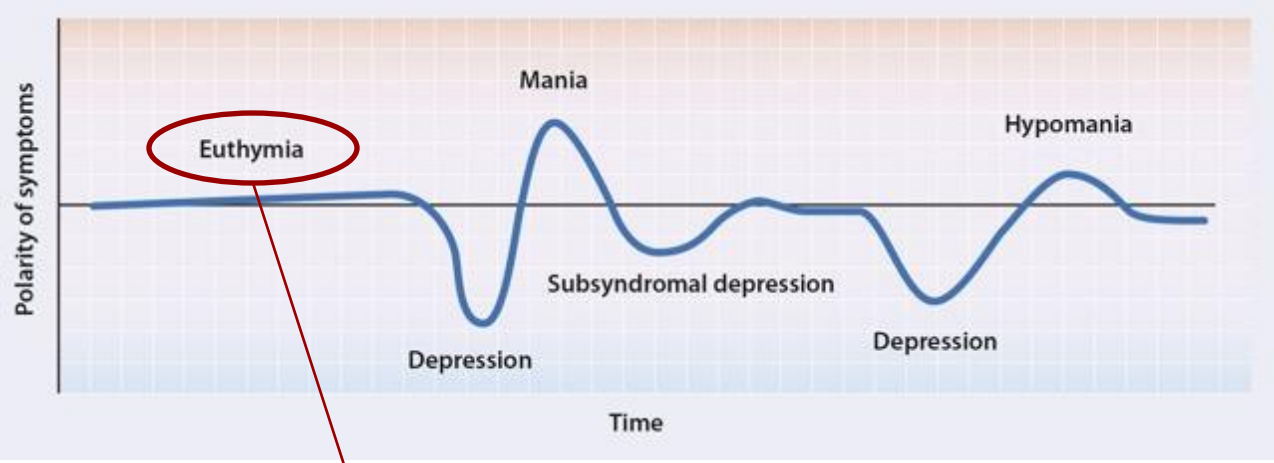
Orienting/Emotion Identification
Automatic Emotion Regulation
Voluntary Emotion Regulation
Regions Implicated in Both Automatic and Voluntary Emotion Regulation

Bipolar Disorder (BD): Hyperactive ventral system → Emotional dysregulation

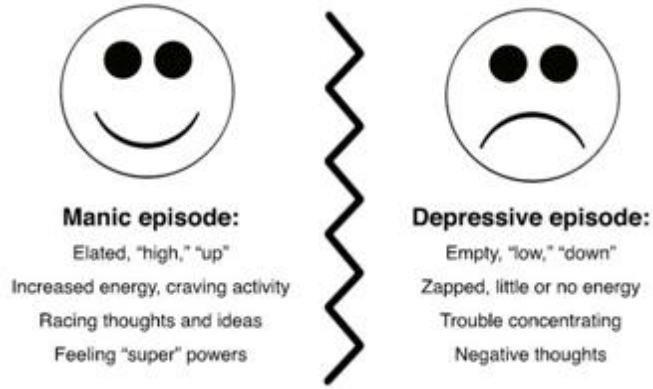
Phillips et al., 2008

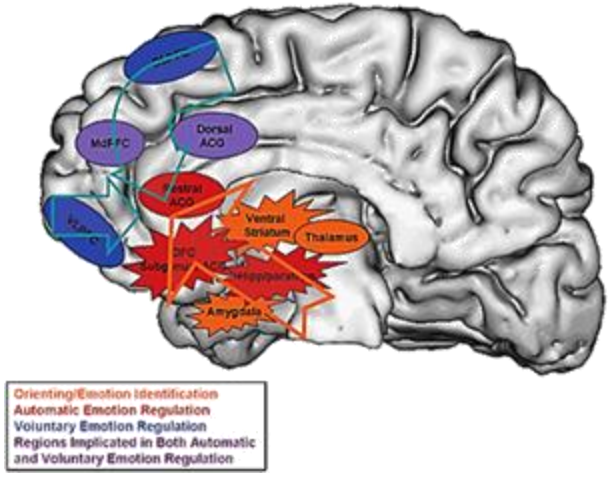
Bipolar Disorder

= severe and chronic mood disease



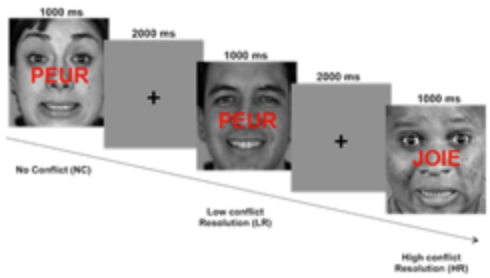
"*Traits*"
characteristics

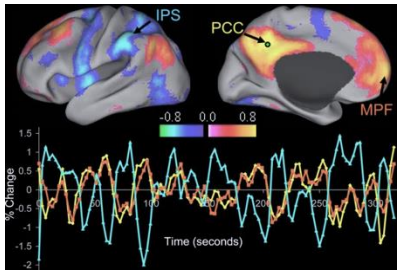




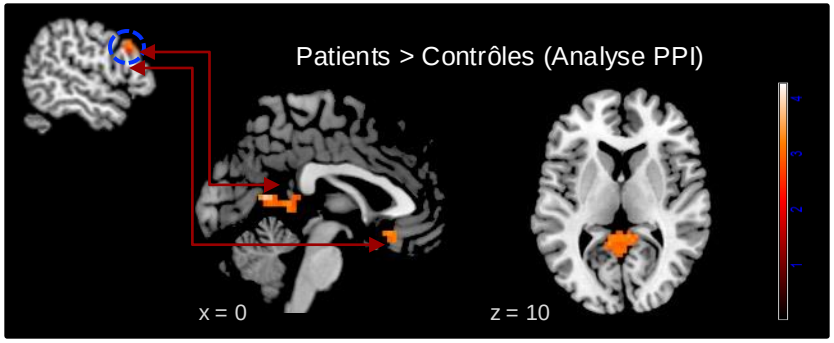
Abnormal functional connectivity in BD

- Emotional Stroop taslk (PPI analysis – seed: dlPFC)



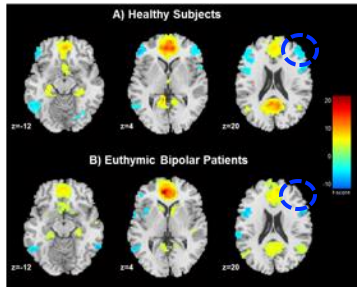


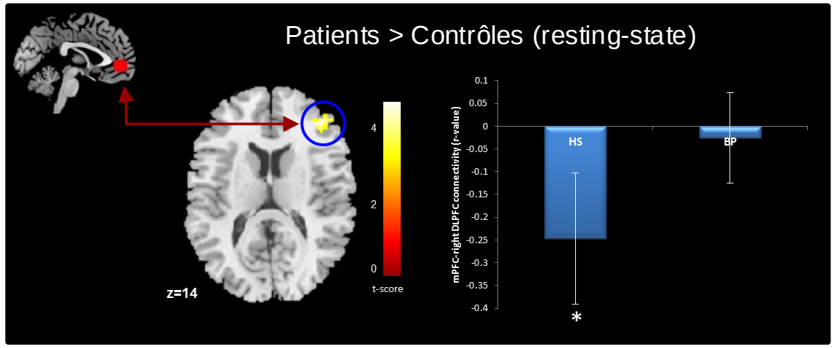
Fox et al., 2005



Favre et al., Plos One, 2015

- Resting-State (seed-to-voxels analysis: vmPFC)



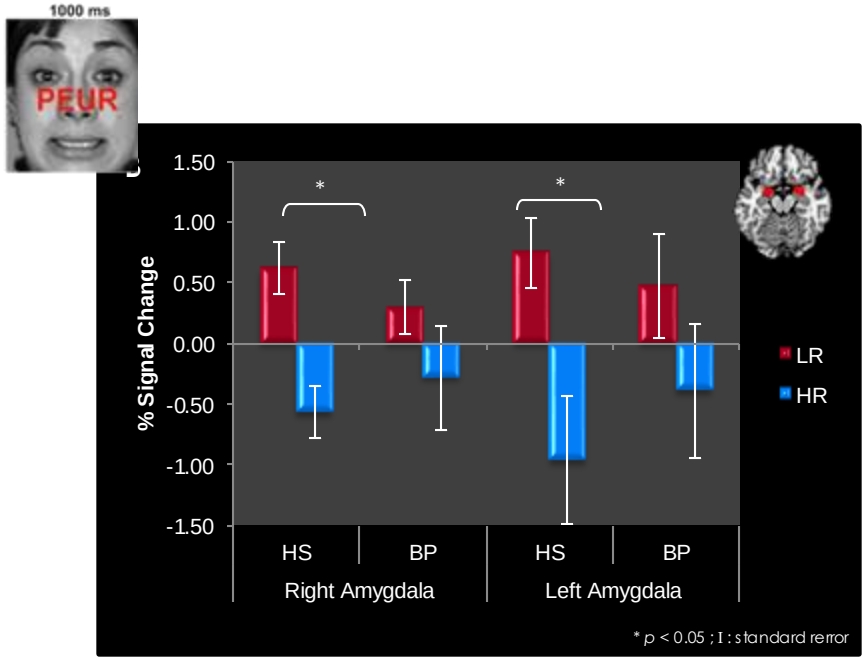


Favre et al, JAD, 2014

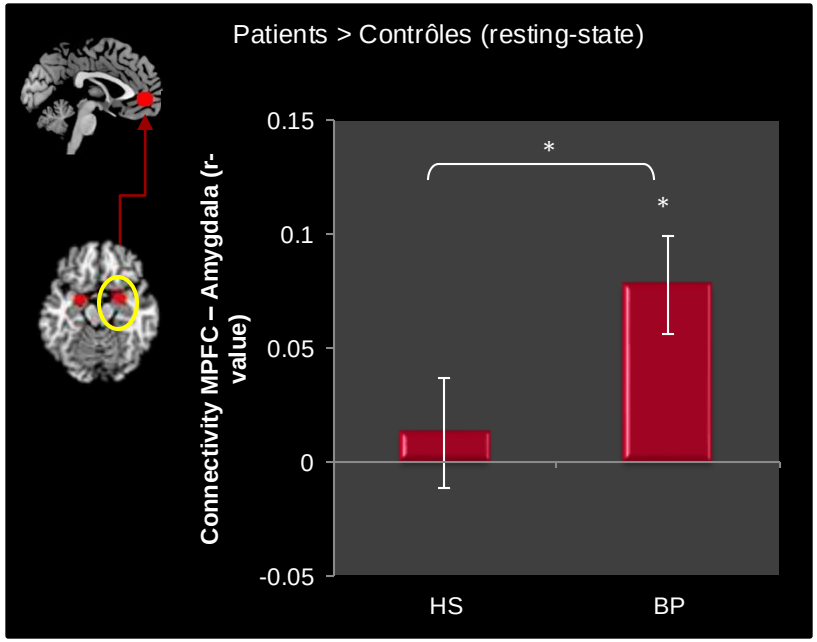
Abnormal functional connectivity between the Central Executive Network and the Default Mode Network in patients with BD both at rest and during cognitive-emotional tasks

Abnormal functionning of the amygdala

- Emotional Stroop Task (PPI analysis – DLPFC)



- Resting-State FC (ROI analysis – vmPFC-Amydala)



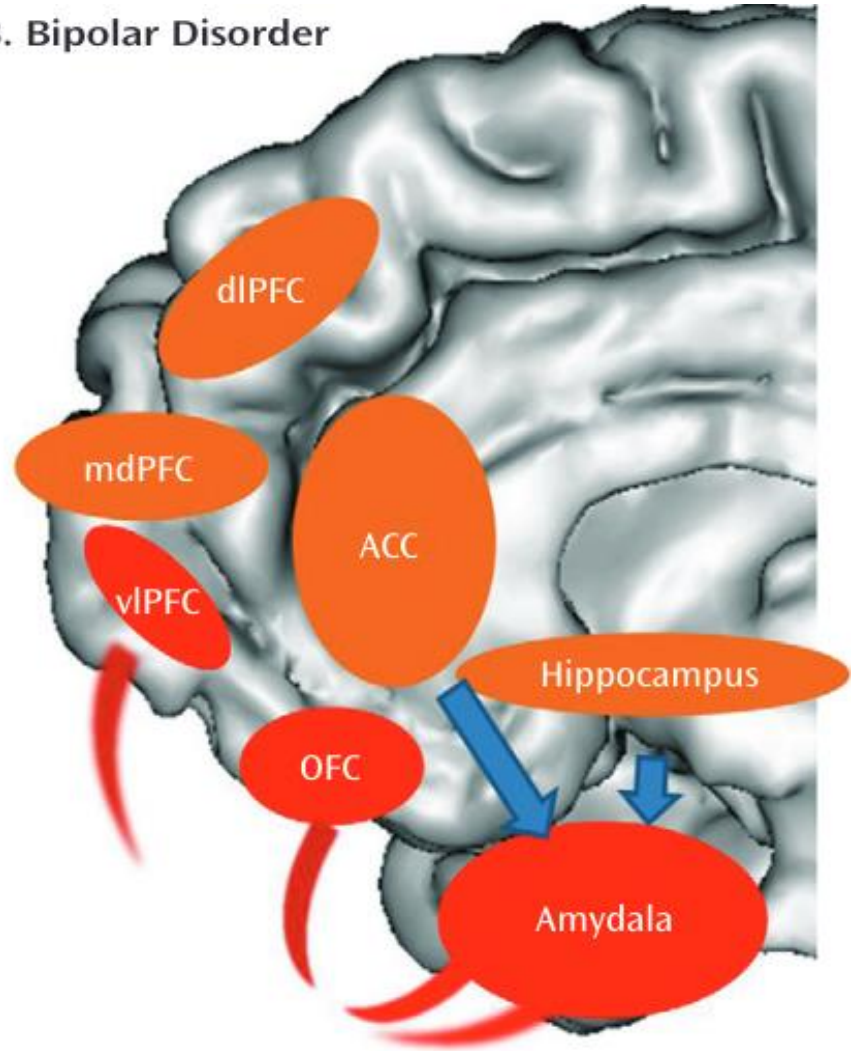
Altered activation during emotional task and abnormal increase functional connectivity with the vmPFC at rest in euthymic patients with Bipolar Disorder vs. healthy controls

Favre et al, JAD, 2014 ; Favre et al., Plos One, 2015

The Amygdala: a key region in the pathophysiology of BD

- Abnormal connectivity with the mPFC[1]
- Hyperactivity in response to emotional stimuli[2,3,4]

But:
- Small samples
- Heterogeneous population
- Various mood states
- No consiration of the subnuclei

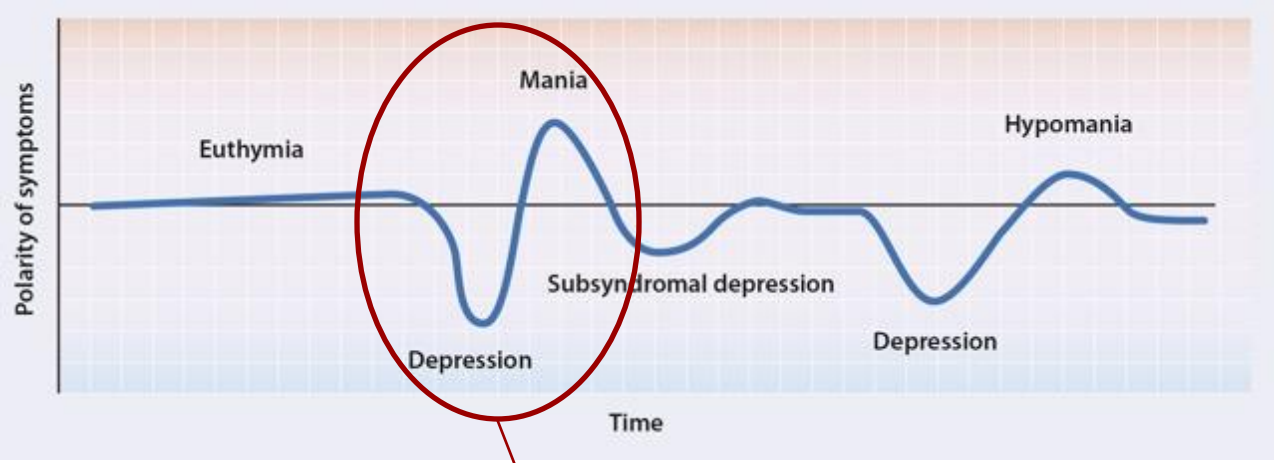


Phillips et Swartz, 2014

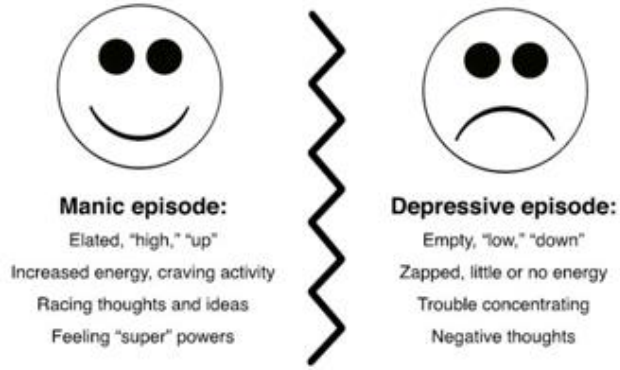
1. *Favre et al, 2014*
2. *Lawrence et al, 2004*
3. *Blumberg et al, 2005*
4. *Strakowski et al, 2012*

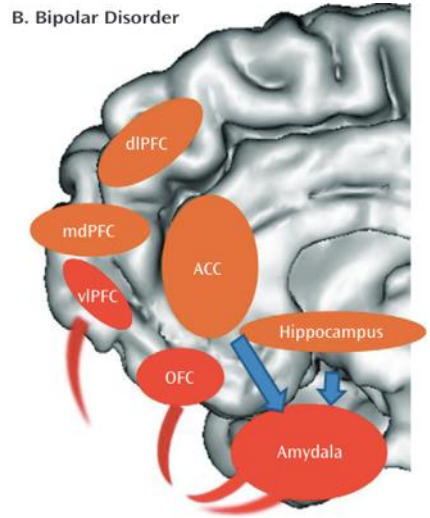
Bipolar Disorder

= severe and chronic mood disease

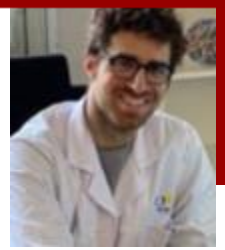


"*States*" characteristics





Phillips et Swartz, 2014



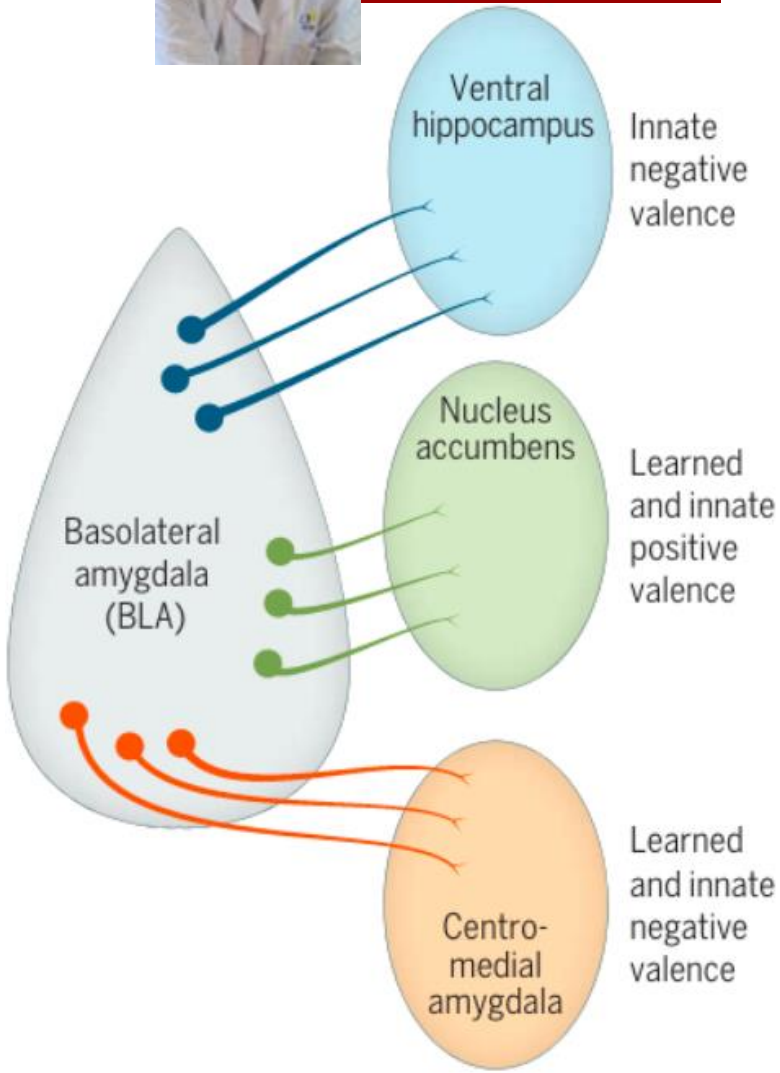
Study objectives
(Krystal et al., 2024)

- Measure of amygdala's subnuleis FC
- Functional networks with coding for specific emotional valence

FC differences between BD patients and HC?

Correlation with the mood state?

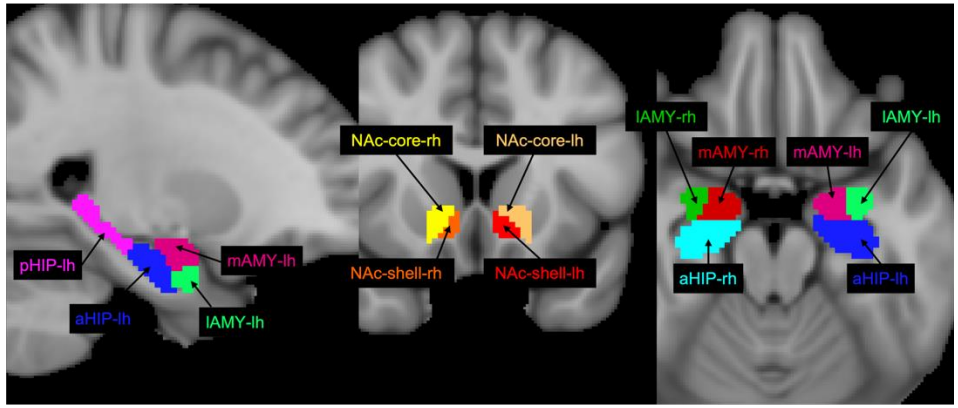
FC differences between subgroup of patients with manic/depressed mood state?



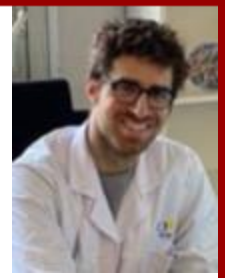
Beyeler, 2016

Study Methods
(Krystal et al., 2024)

- Multicentric study: Créteil, Grenoble, Geneva
- 127 BD patients and 131 healhy controls (18-65 yrs)
- Preprocessing with MRI QC and fMRI prep
- Resting-state functionnal connectivity
  - ROI-to-ROI analyses
  - Tian's subcortical atlas (2020)
  - 12 ROIS
  - Computation of functional connectivity matrices (Nilearn)

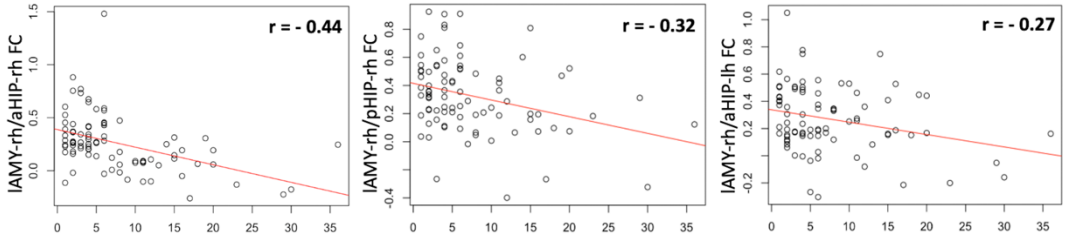


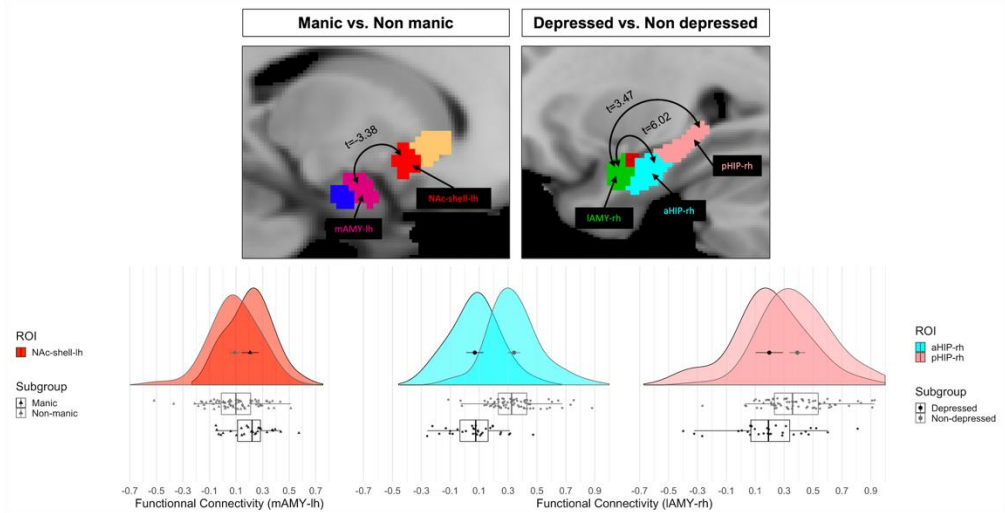
- lateral (**lAMY**) medial (**mAMY**) nucleis of the amygdala
- Anterior (**aHIP**) and Posterior (**pHIP**) Hippocampus
- Central (**NAc-core**) and peripherical (**NAc-shell**) parts of the nucleus accumbens



Study Results
(Krystal et al., 2024)

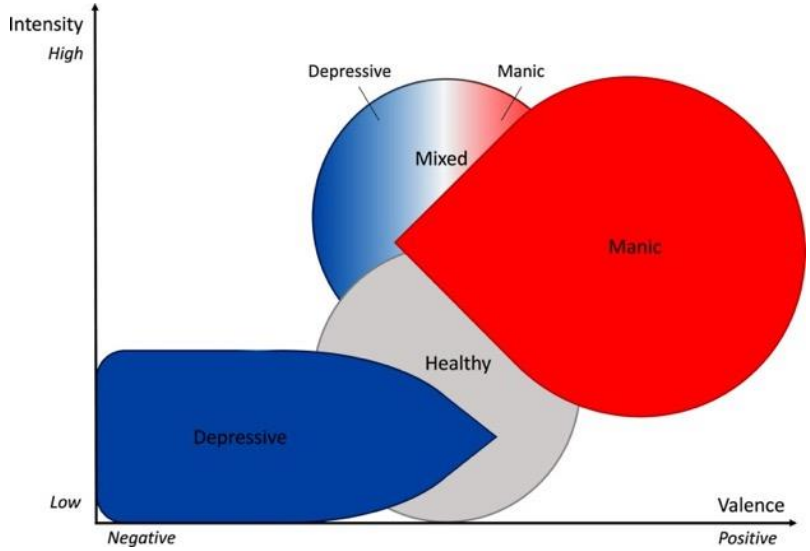
- No difference between BD patients and HC
- Significant correlations between depression scores and lateral AMY – HIP connectivity
- Increase FC medial AMY – Nac in manic vs. non manic patients
- Decrease FC lateral AMY – HIP in depressed vs. non depressed

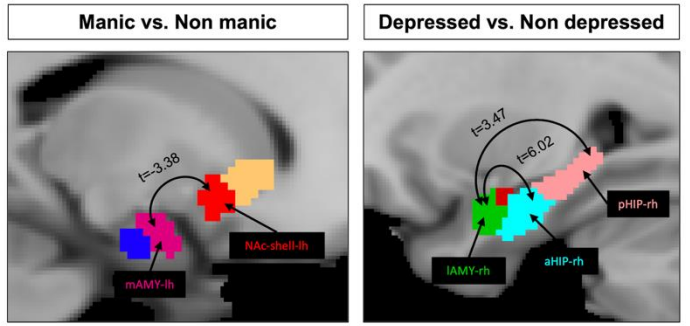




Discussion
(Krystal et al., 2024)

- Valence specific brain networks are correlated with mood states of bipolar disorder
- Important to consider amygdala subnuclei ++
- Limits: retrospective study, patients with low symptoms levels, comorbidities (anxiety++), subgroups with small samples
- Need further prospective studies in unipolar depression, manic patients and schizophrenia





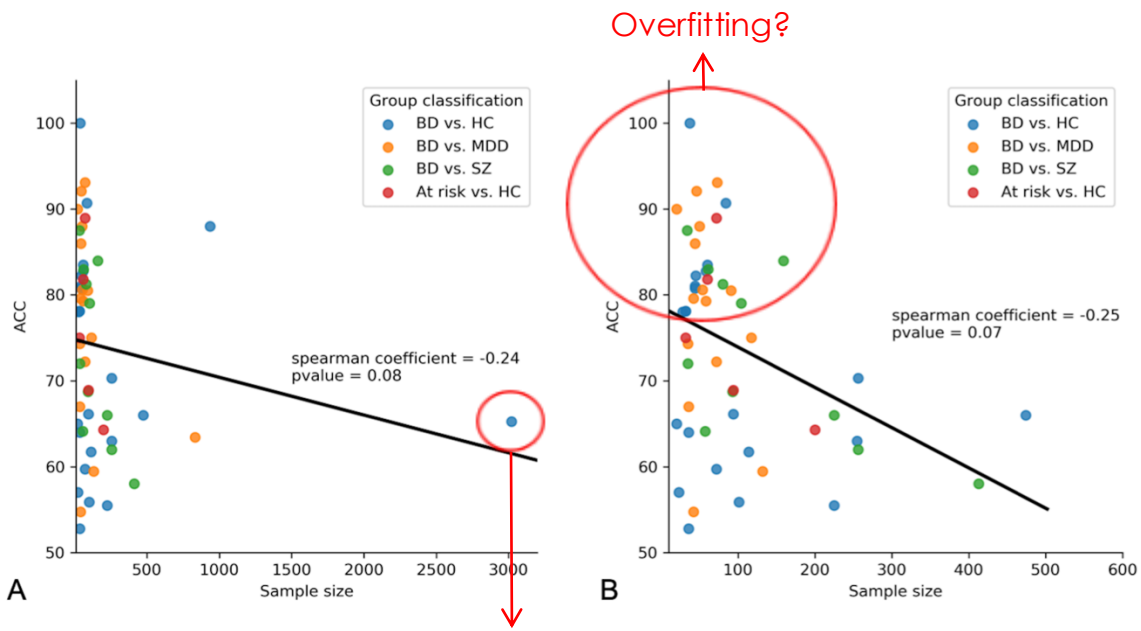
Neuroimaging-based Prediction of Bipolar Disorder

Can we use machine learning to better diagnose bipolar disorder?

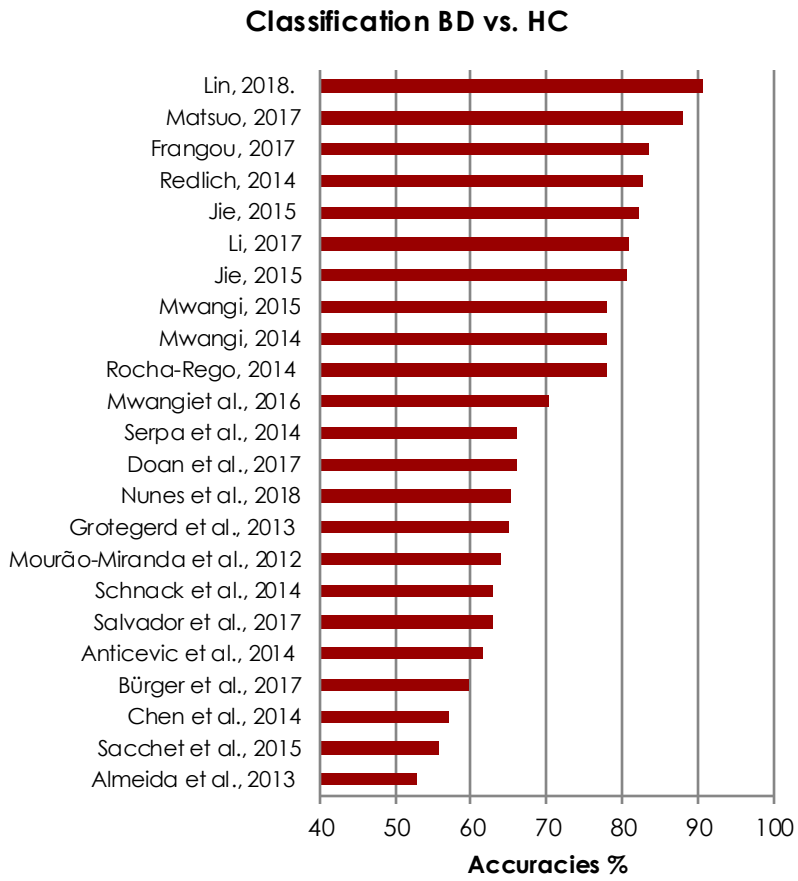
Systematic literature review:

"Will machine learning applied to neuroimaging in bipolar disorder help the clinician? A critical review and methodological suggestions"

- 24 studies BD vs. Healthy controls
- 16 studies BD vs. Major depressive disorder
- 12 studies BD vs. Schizophrenia



Nunes et al., 2020; ENIGMA; N>3000



Claude, Houenou, Duchesnay & Favre, 2020 Bipolar Disorders

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

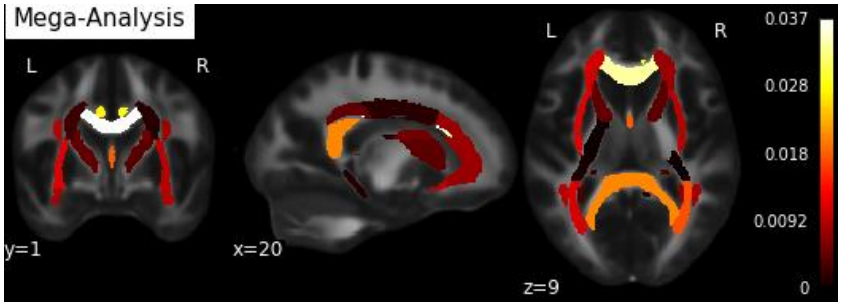
Power failure: why small sample size undermines the reliability of neuroscience

ENIGMA Bipolar Disorder DTI Working Group (N =3033)

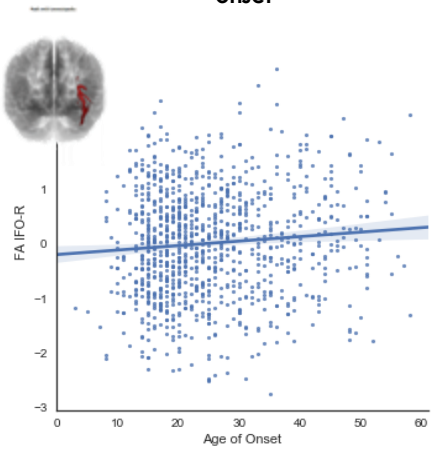
➔Diffusion-weigthed MRI data from 26 international cohorts (harmonized pipeline)

ENIGMA – BD : DTI Results
(N > 3000; 26 centers worldwide)

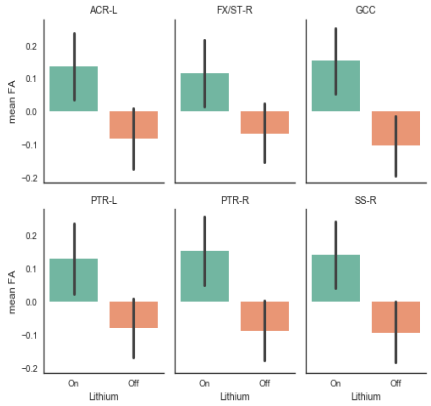
Univariate statistics (Mega- and Meta-analyses)
→ decreased FA on 29/44 tracts



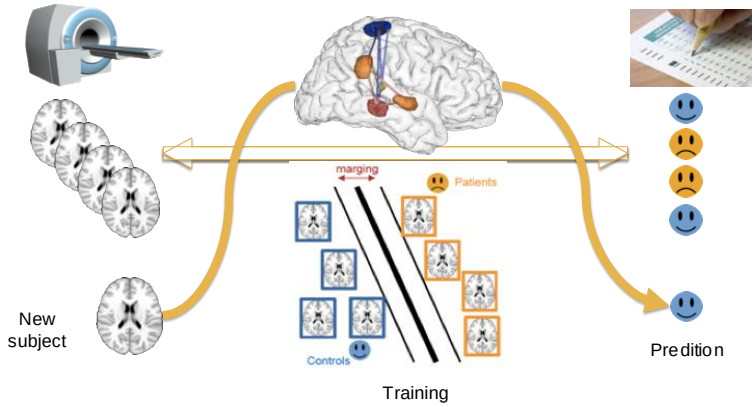
- **IFO-R more preserved when later onset**



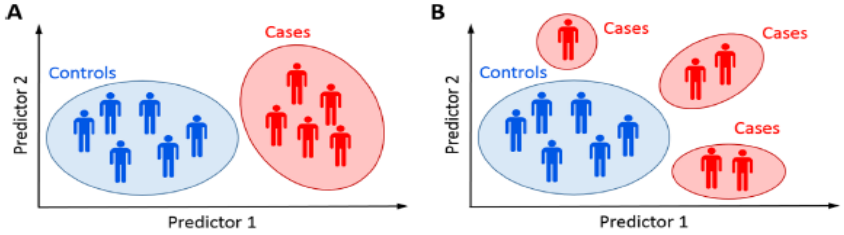
- **Patients on lithium with higher FA**



Diagnosis prediction and stratification with Machine Learning?

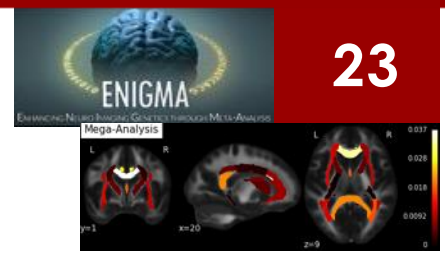


© E. Duchesnay



Favre, et al, 2019, Neuropsychopharmacology

Marquand et al., Biol. Psy., 2016

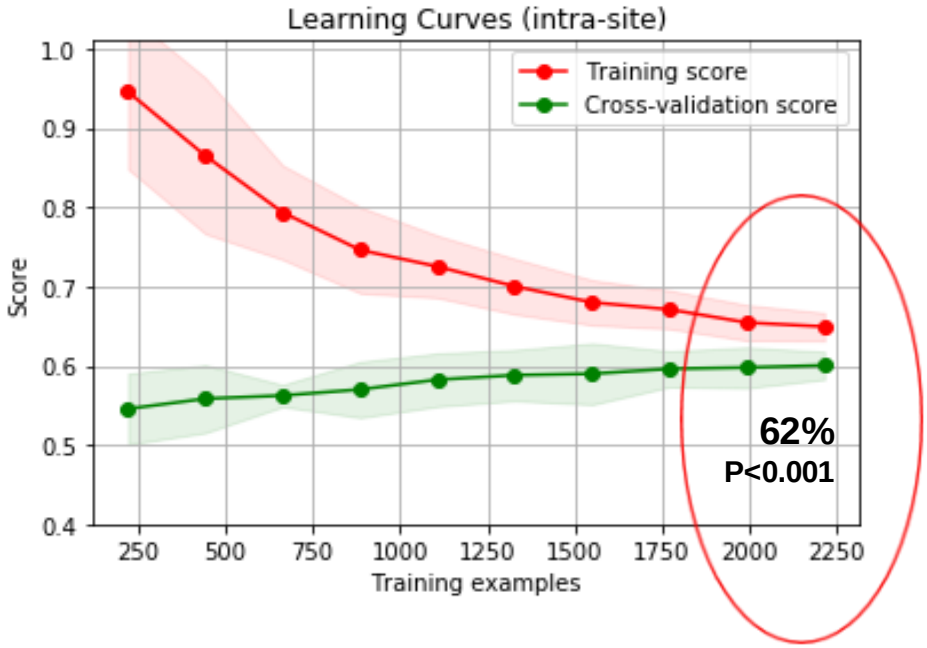


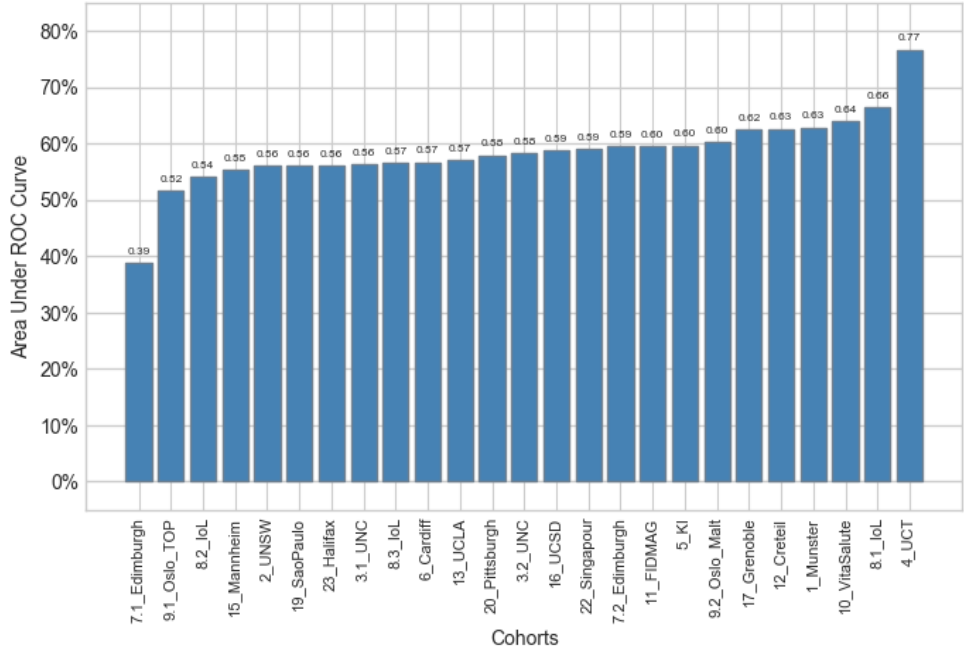
ENIGMA BD-DTI:
Supervised Machine Learning

Method: Linear SVM with nested double CV (SciKit learn)

Intra-site (5 folds-CV):
ROC-AUC = 62.22%(62.09% / 58.35%)

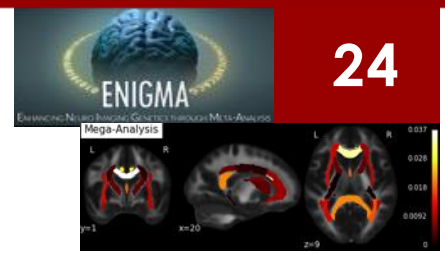
Leave one-site-out (26 folds):
ROC-AUC = 57.46% (60.29% / 54.63%)





➔ **The accuracy of the classification is highly significant but the classification performance is « moderate »**

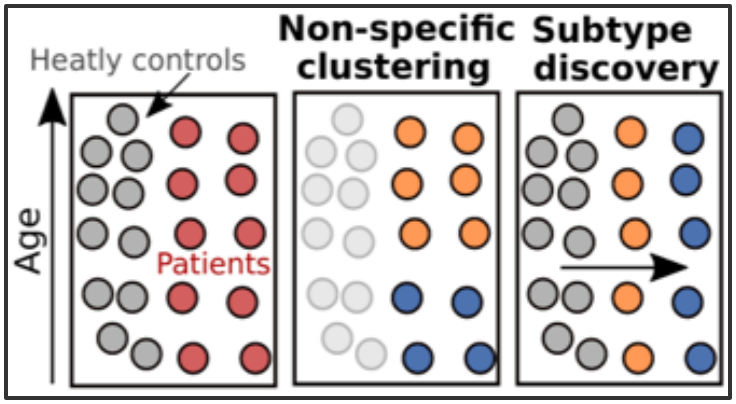
Favre et al, in prep



ENIGMA BD-DTI

Unsupervised Machine Learning

Stratification with machine Learning



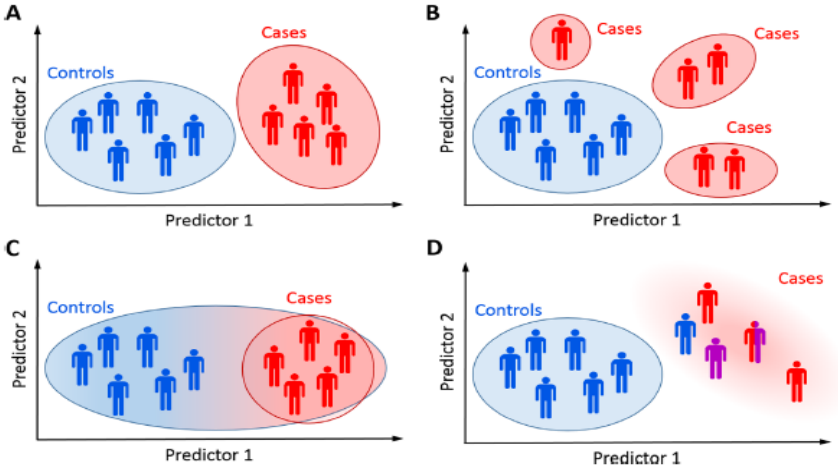
UCSL = Unsupervised Clustering driven by Supervised Classification (***Louiset et al., 2021***)

- Measures: FA of the 43 tracts
- UCSL algorithm
- Comparision of clinical characteristics

- No sign. differences in age / sex / site
- FA (all tracts): Cluster 1 > Cluster 0
- **Proportion of patients under Lithium significantly higher in Cluster 1**

Favre, Louiset* et al, in prep.*

Discussion : Prediction and Stratification of Mood Disorders



- Robust but moderate classification performances of BD diagnosis based on structural MRI with big cohorts (N>3000)
- Adding more modalities might help the algorithms → deep learning?
- Big impact of the medication

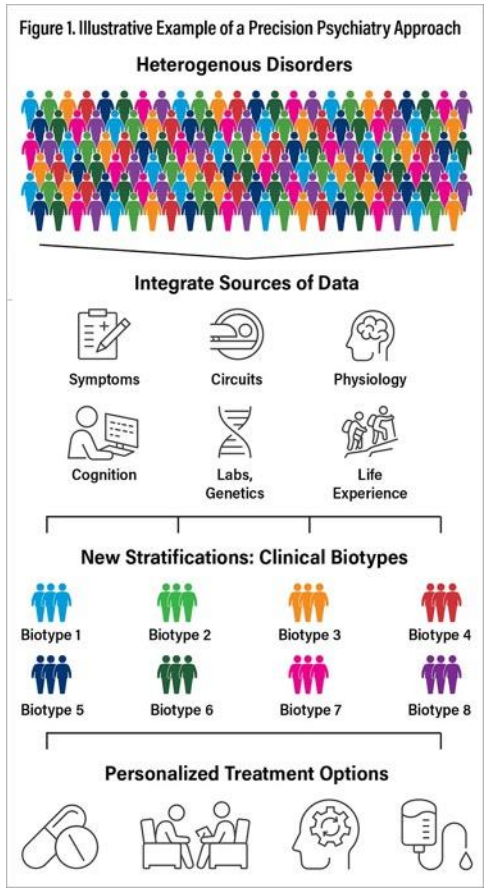
➔Need to better understand the heterogenity of the disorder

➔Need for well phenotyped big cohorts

Discussion and perspectives

Integration of multi-modal and longitudinal data

Challenge n°1: Disorders stratification
Challenge n°2: Predict disease evolution
Challenge n°3: Predict treatment response



- Development of the **"*FrenchMinds*" cohort**
- **Multicentric, multimodal & longitudinal study**
- **Targeted conditions**: severe recurrent depression, bipolar disorder, schizophrenia, first psychotic episodes, autism (without intellectual disability)
- **Objective**: precision psychiatry, advanced diagnostic tools
- **Identification of biomarkers** to better classify patients
- **Collected data**: clinical, genetic, electrophysiological, brain imaging, environmental

PROPSY: One step further towards Precision Medicine in Psychiatry

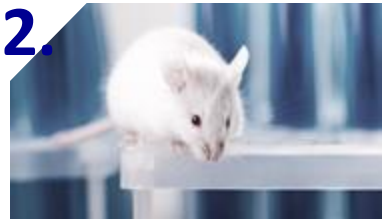
WP 6 Transversal for integration and implementation of results

1.

Building the cohort FRENCH-MINDS with multimodal databases to identify homogenous clusters of patients

WP 1: FRENCH-MINDS
a unique cohort of patients with mood/psychotic/neurodev disorders to build multimodal databases (Clinical, genomics, metabolomics, immune, brain imaging, Ecological Momentary Assessment…) and identify biomarkers/algorithms for patient stratification

2.



Physiopathology underlying homogeneous subgroups of psychiatric disorders

WP 2: Developing pre-clinical studies towards mechanisms discovery

3.

New diagnostic tools and therapeutic strategies towards precision medicine

WP 3: Supporting clinical trials towards diagnostic tools and treatments discovery in e-health, Immuno–modulation, Non invasive brain stimulation, Invasive brain stimulation, Physical health ,

4.

Development of a new French biomedical mental health sector,
Incl. digital, biotech, medtech, pharma, medical devices etc.

WP 4: Creating tools to develop a new biomedical sector

- Digital tools
- Electrophysiology
- Algorithm
- Probiotic
- Immuno-modulation
- Brain stimulation

5.

Education, awareness, attractiveness, and policy briefs

WP 5: Education and implementation

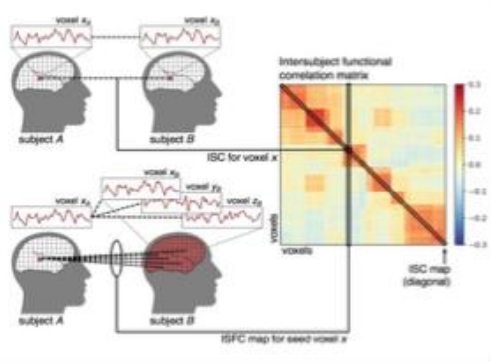
- Public and stakeholder Information
- Summer Schools
- University diploma
- Academy (Neuromodulation, psycho-social therapy)
- Knowledge hub

➔ https://pepr-propsy.fr/2024/09/30/frenchminds/

PROPSY : MRI protocol

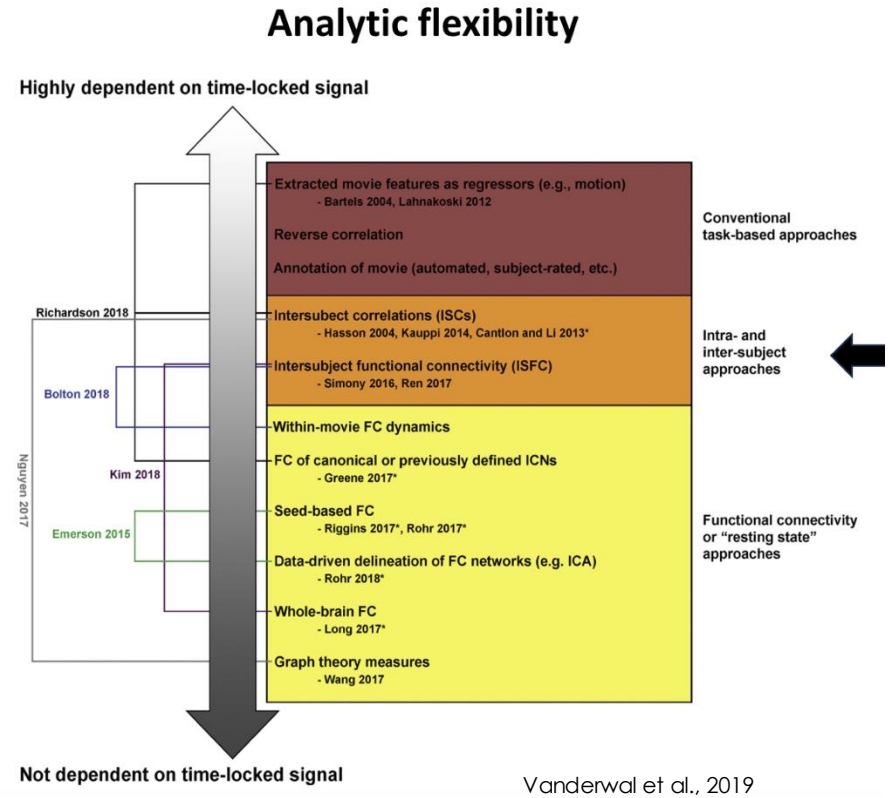
- 3T sequences: 3DT1, FLAIR, SWI, fMRI Movie Data, diffusion
- 7T sequences: MP2rage, fMRI tâche, spectroscopie, IRM de capture

Naturalistic stimuli : movies + PEER data



(Nastase et al. 2019)

(Alexander et al. 2017)

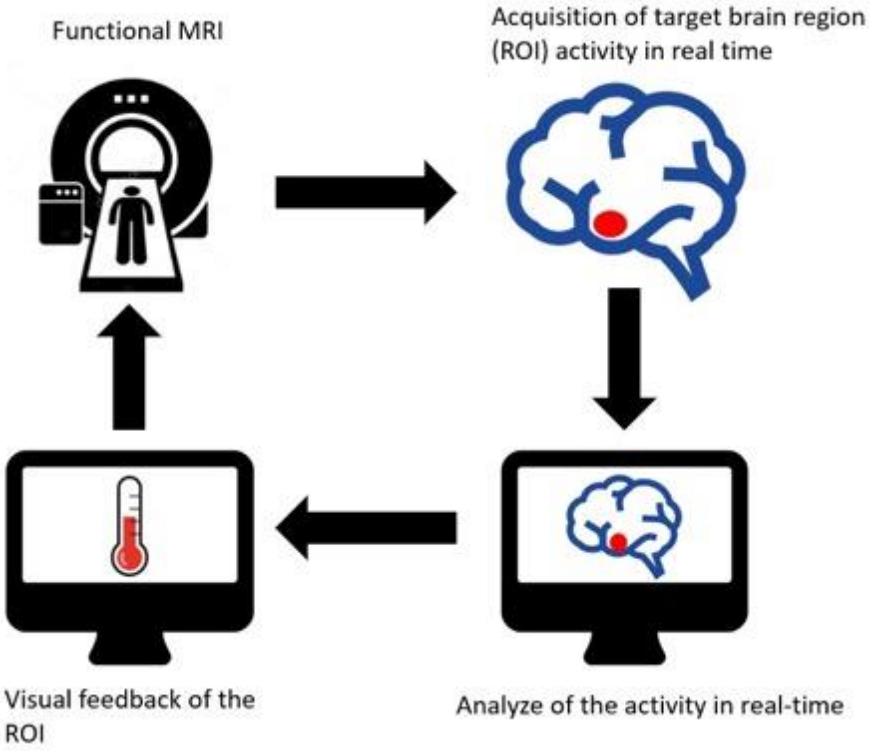


Vanderwal et al., 2019

Neuroimaging-based treatment for Bipolar Disorder

Can we use neuroimaging discoveries to manage symptoms of mood disorder?

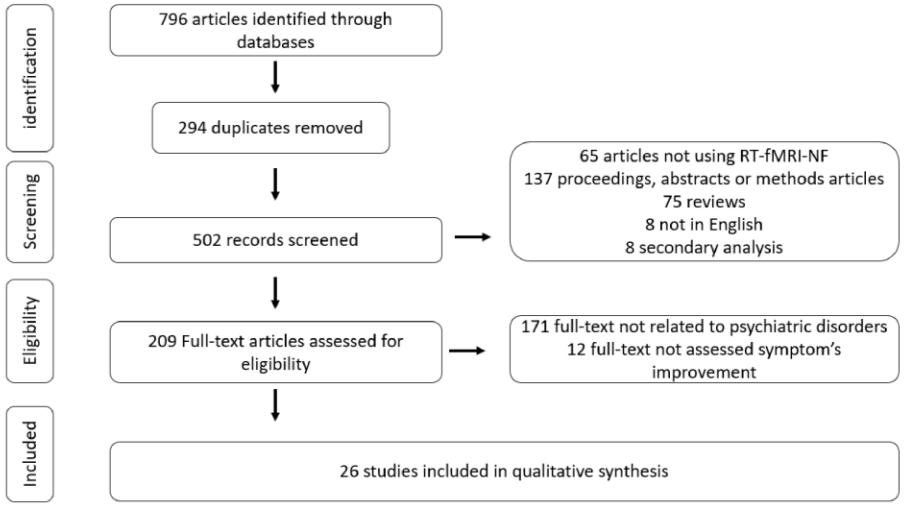
Real-time fMRI Neurofeedback

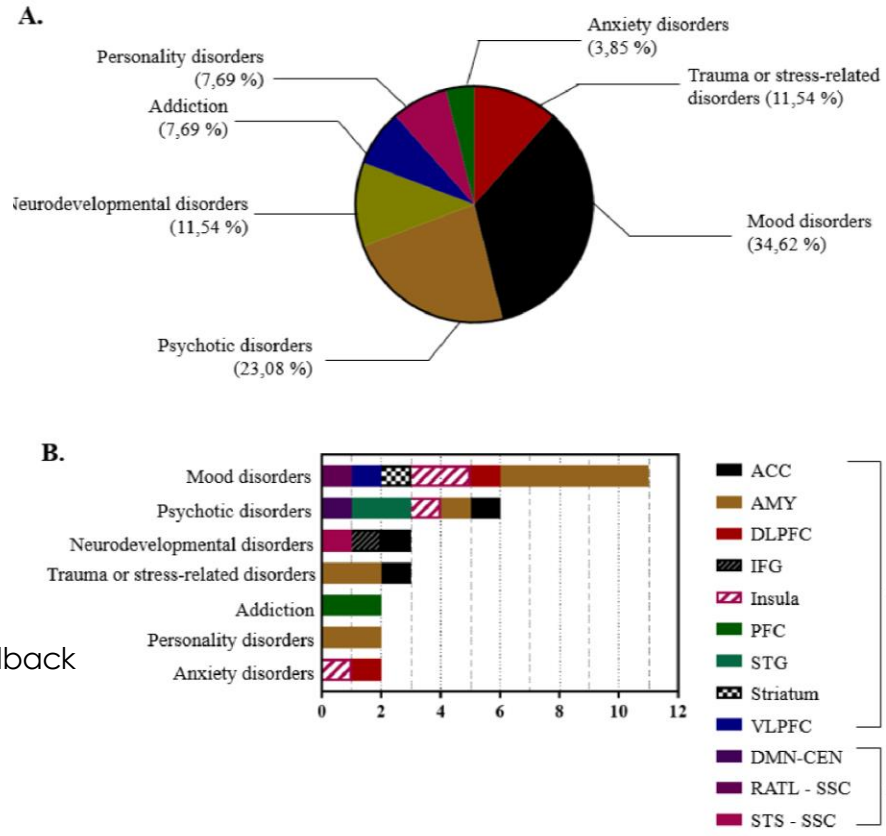


- RT-fMRI-NF is a newly developed technique
- Participants are learning to control their own brain activity through the feedback signal
- fMRI allows to record the activity of **deep brain structures**
- Efficacity demonstrated in epilepsia, chronic pain, hemispatial neglect, and **psychiatric symptoms**!

Systematic review

"Real-time fMRI neurofeedback as a new treatment for psychiatric dirsorders?"



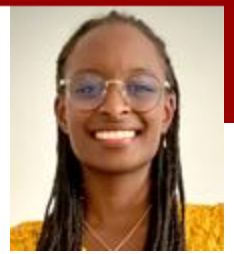


- 19 studies showing **significant symptoms improvement** after neurofeedback
- 12 with non significant improvment
- 1 with no superior effect relative to the control (sham) group

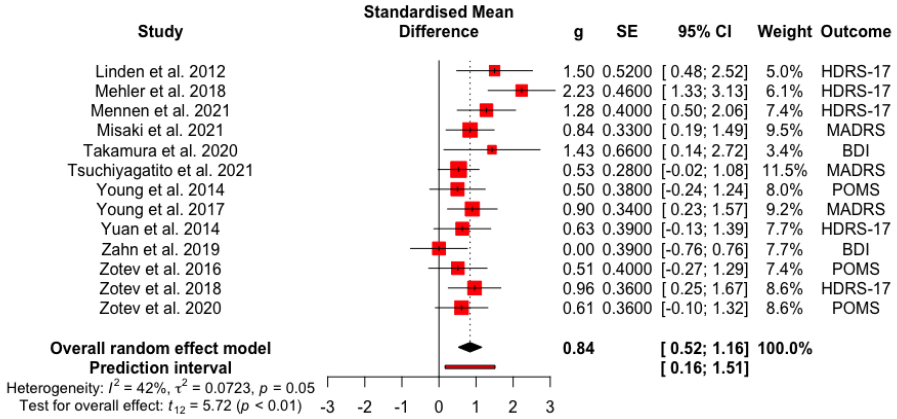
Pindi, Houenou, Piguet & Favre, 2022, Progress in Neuropsychopharma. and Biol. Psy

Meta-analysis

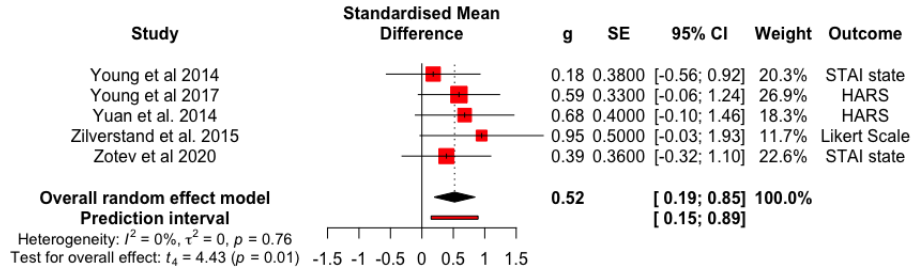
"Real-time fMRI neurofeedback as a new treatment for psychiatric dirsorders?"



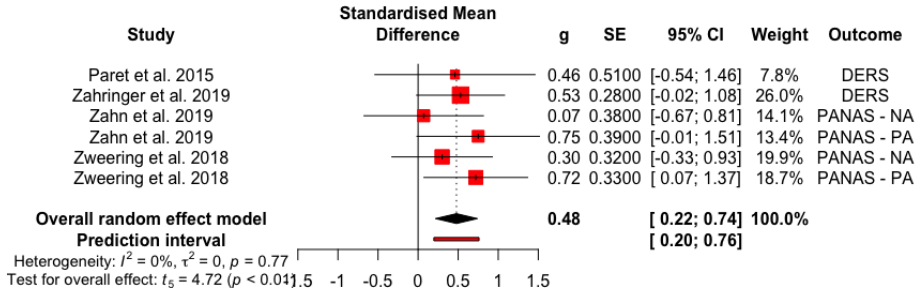
Depression



Anxiety



Emotion regulation



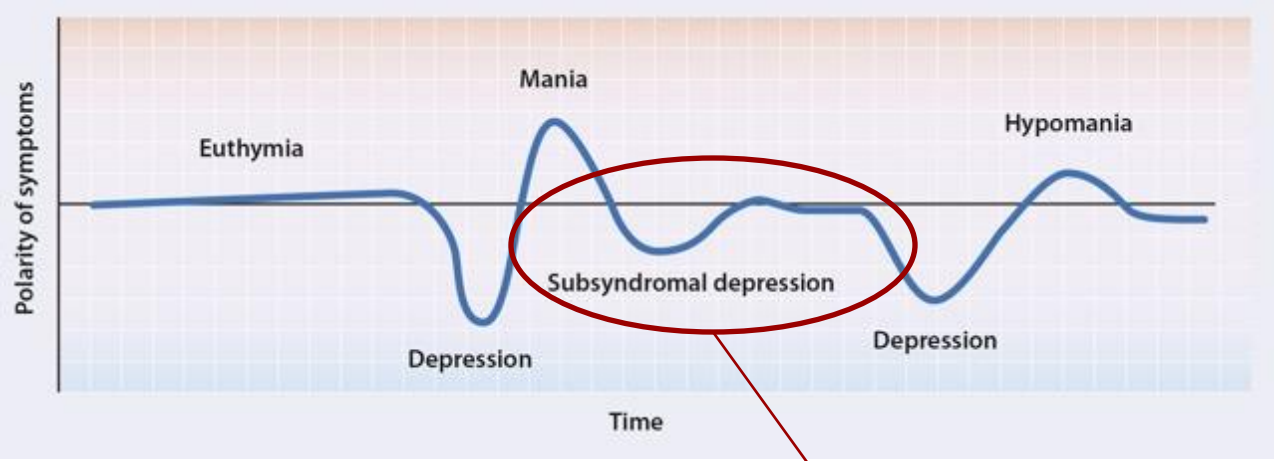
- Large effect size on depressive symptoms
- Medium effect size on anxiety and emotion regulation

BUT NO STUDIES ON BIPOLAR DISORDER SO FAR!

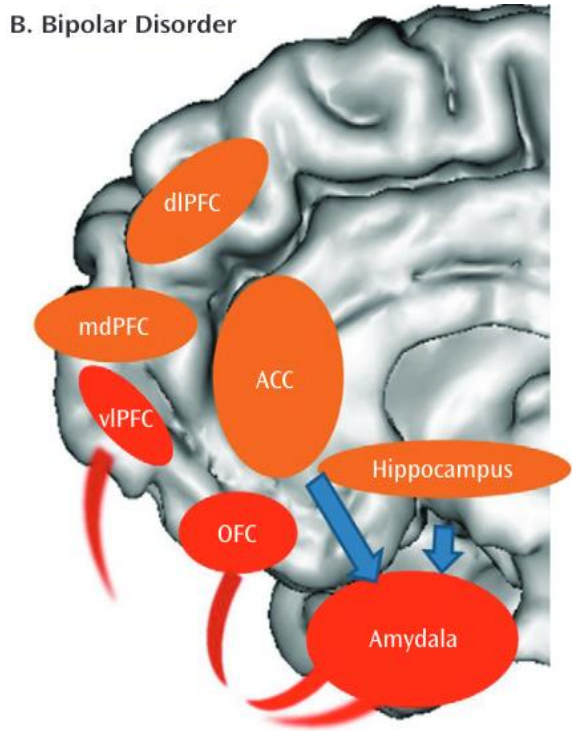
Pindi, Houenou, Piguet & Favre, 2022, Progress in Neuropsychopharma. and Biol. Psy

Bipolar Disorder

➔ What treatment?

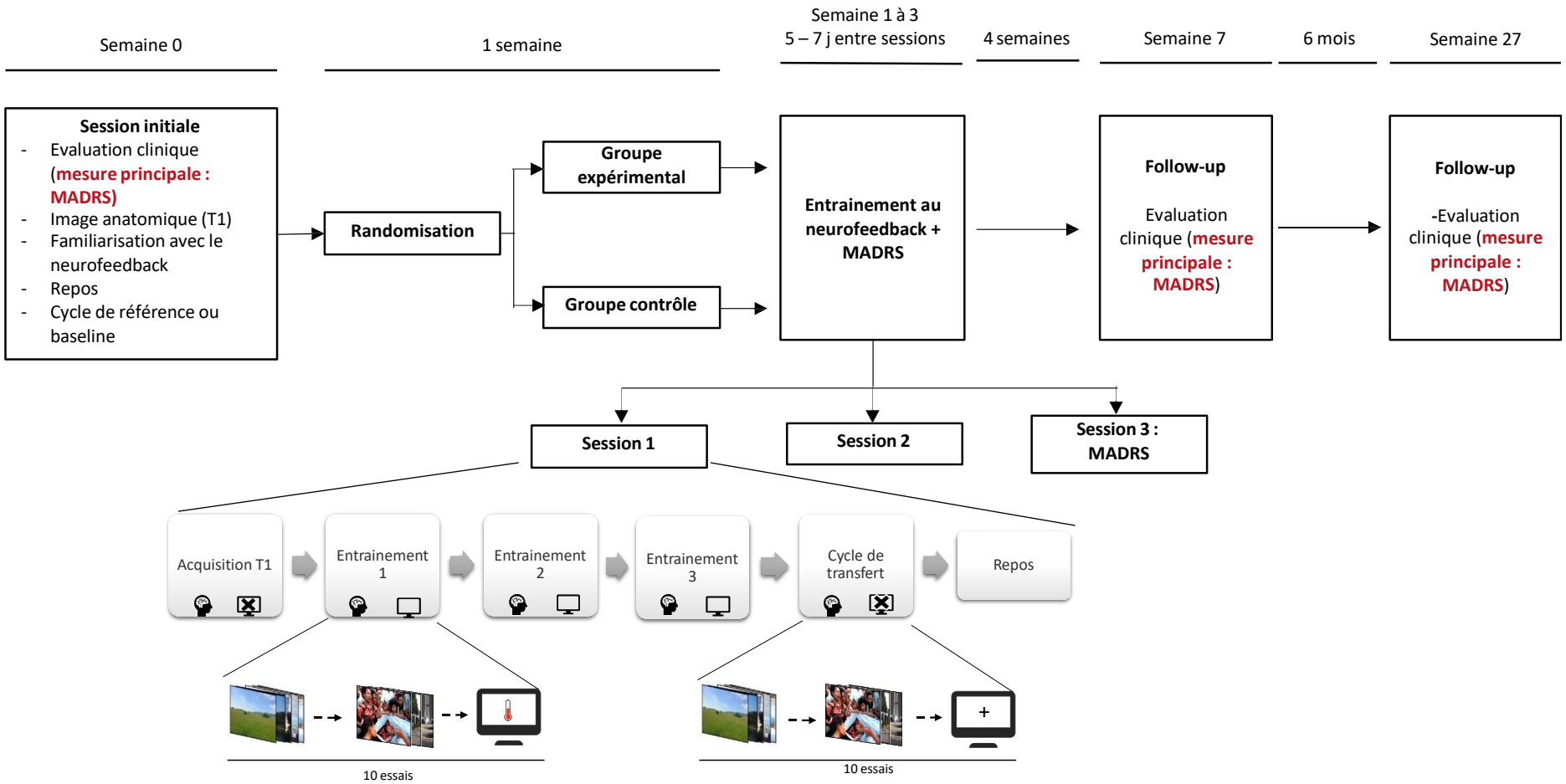


Therapeutic options?
→ **Neurofeedback**?



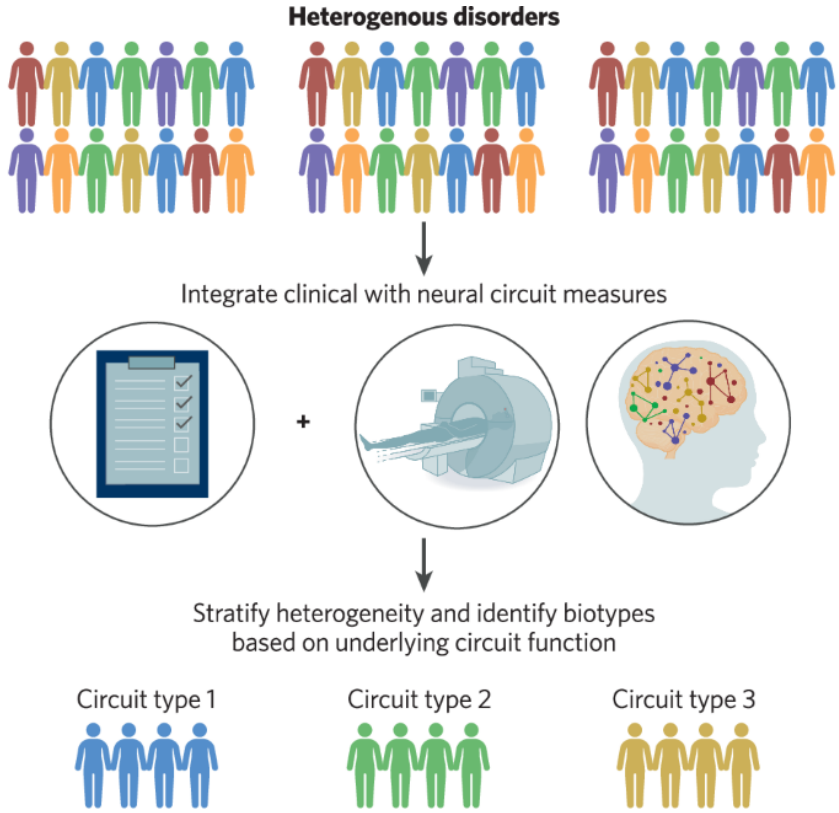
Phillips et Swartz, 2014

NeuroFeed-BD : Essai randomisé contrôlé en double aveugle



PHRC-N 2018 (Favre / Houenou) ; Pamela Pindi (PhD project)

Challenges in brain imaging of mood disorder



- **Identify neurobiological markers** that can help to optimize the diagnostic accuracy
- **Refine, individualize and personalize the therapeutic approach** by identifying markers of resistance and response to the treatments

➔ **PRECISION PSYCHIATRY**