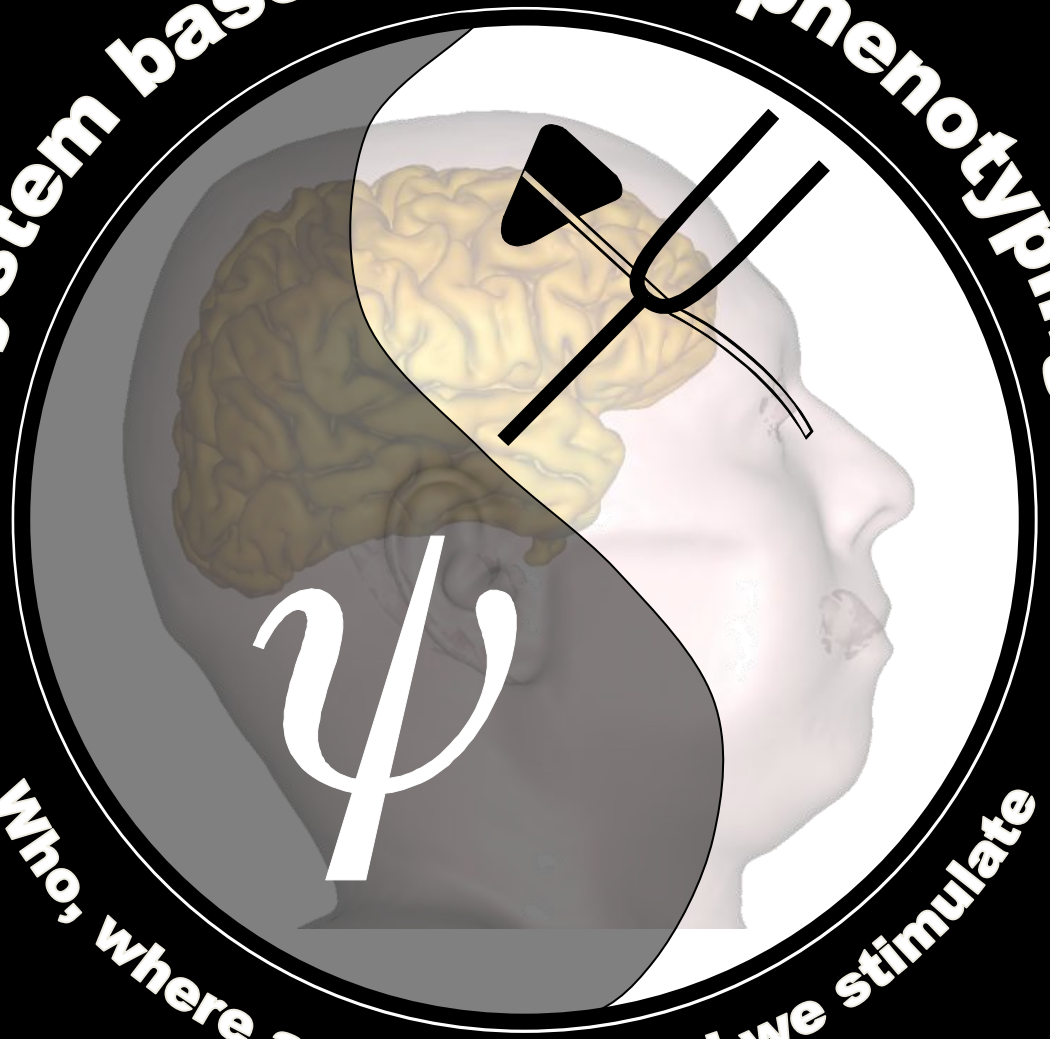
System based clinical phenotyping

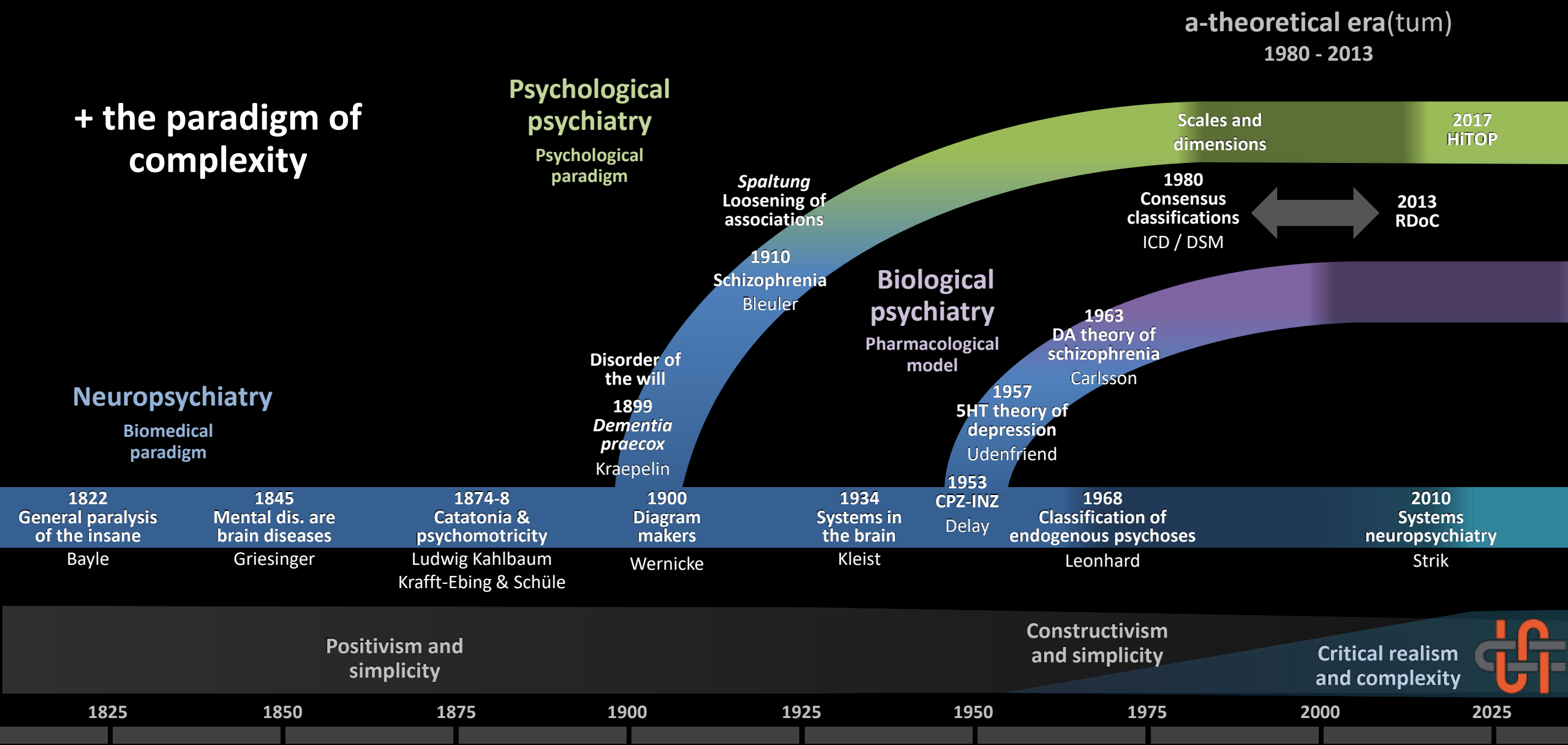


Who, where and how should we stimulate

Foucher JR, de Billy C, Jeanjean LC, Mainberger O,
Schorr B, Clauss JME, Obrecht A, Weibel S, Berna F
CEMNIS & CES – HUS / iCube, SAGE & U1114 Strasbourg - France

Personalization of neuromodulation
Dormegny-Jeanjean & Foucher - 10th February 2023
Strasbourg - France

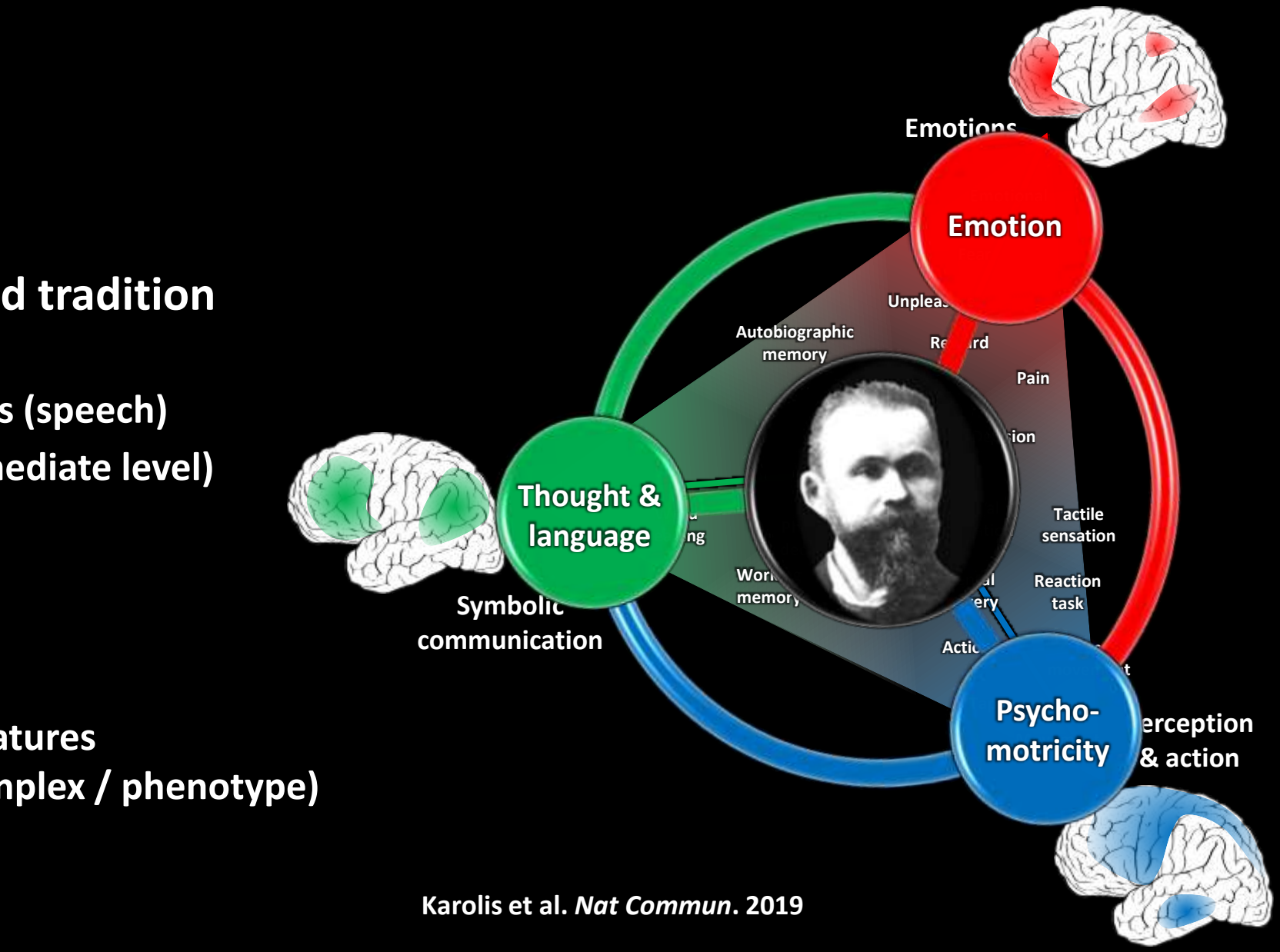
Continuation of the neuropsychiatric research program



Domains, macrosystems, systems...

- 3 behavioral domains – old tradition
  - Emotion (valence)
  - Though and related actions (speech)
  - Psychomotricity (as intermediate level)
  - ± Drive (appetitive)

- Typological definition
  - Highly distinctive set of features (syndrome / symptom-complex / phenotype)

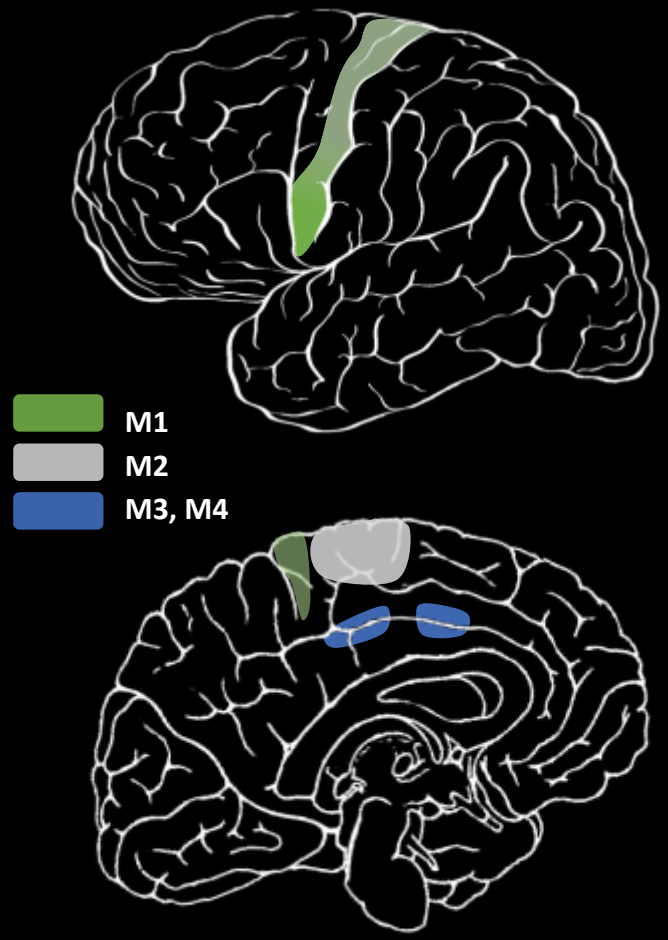


Karolis et al. *Nat Commun*. 2019

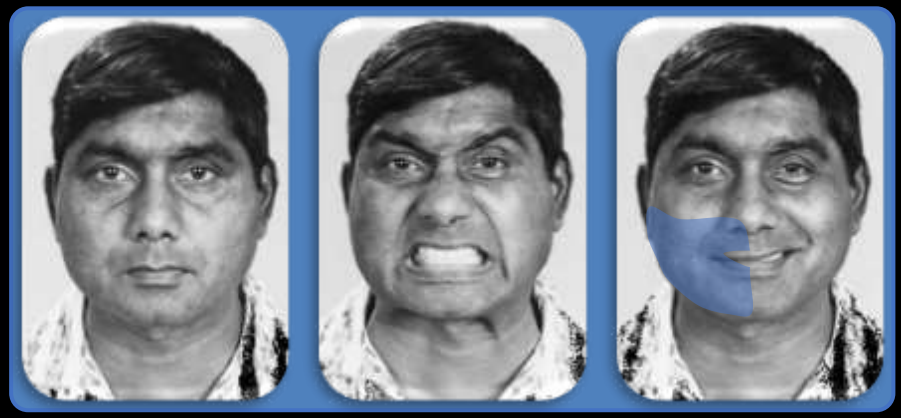
Psychomotricity : example of expressive movements

- **PM systems: automatic (innate ?) systems for interpersonal behaviors**
  - **Emotional expression**
  - **Social reactions (orienting, responsive grasping)**

Double dissociation
Neuropsychiatric PM ≠ ICD/DSM version



Neutral **Intentional** **Expressive**



Foucher et al. 2022

Catatonia = dysfunction of psychomotor systems

- PM systems: automatic (innate ?) systems for interpersonal behaviors
  - Emotional expression
  - Social reactions (orienting, responsive grasping)
- Interpretation of ‘affective flattening’
  - Flattening of emotion (ICD/DSM)
  - Or hypo-functining of (expressive) PM systems?

From University of California (1961)

Foucher et al. 2022

Catatonia = dysfunction of psychomotor systems

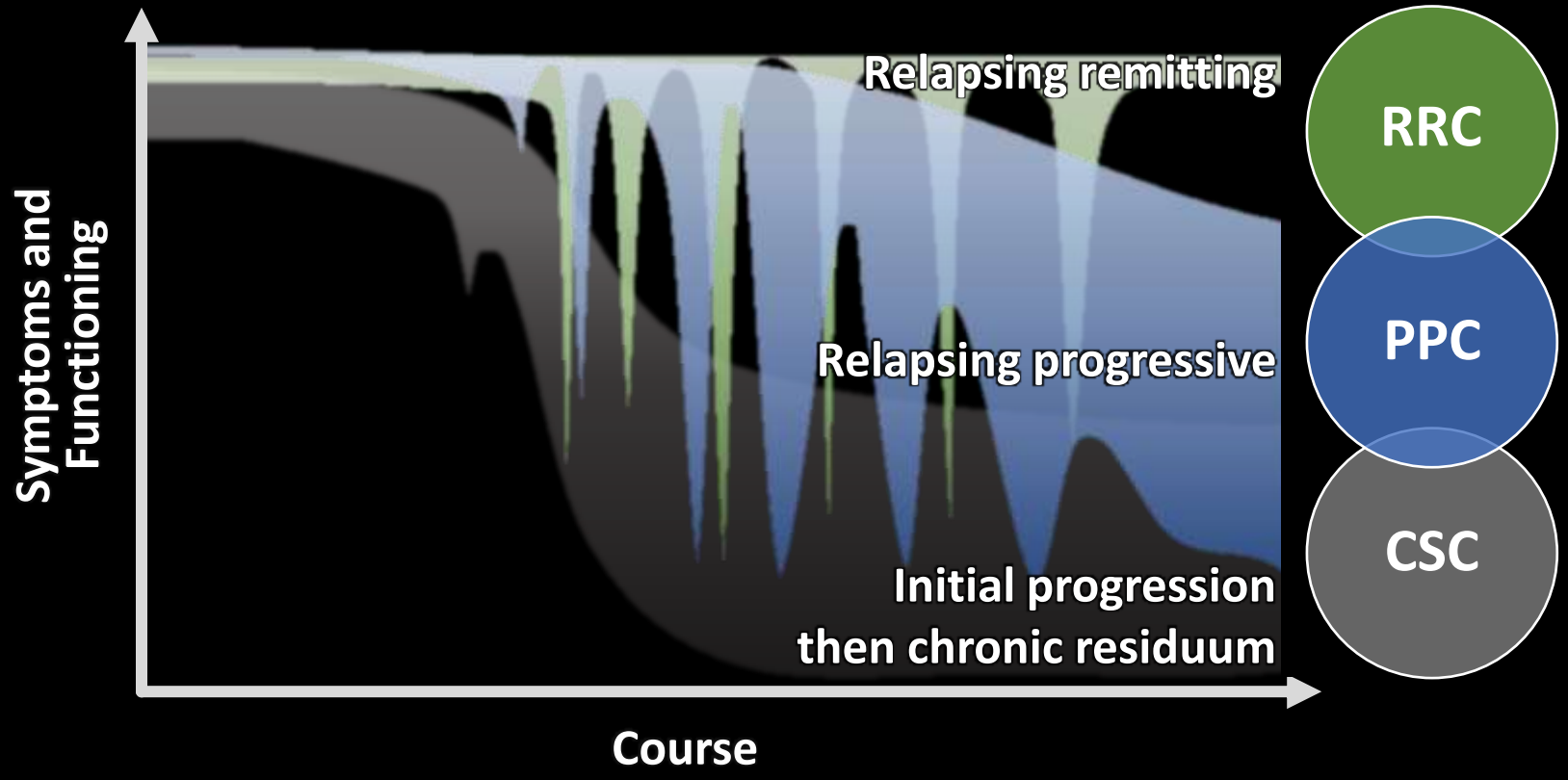
- **PM systems: automatic (innate ?) systems for interpersonal behaviors**
  - Emotional expression
  - Social reactions (orienting, responsive grasping)
- **If intrinsically dysfunctional ('para'-functioning)**
  - Hyperkinetic parakinesia (emotional sys. → grimacing)
  - Parakinetic psychomotricity

From Arte miniseries 'P'tit Quinquin' by Bruno Dumont (2014)

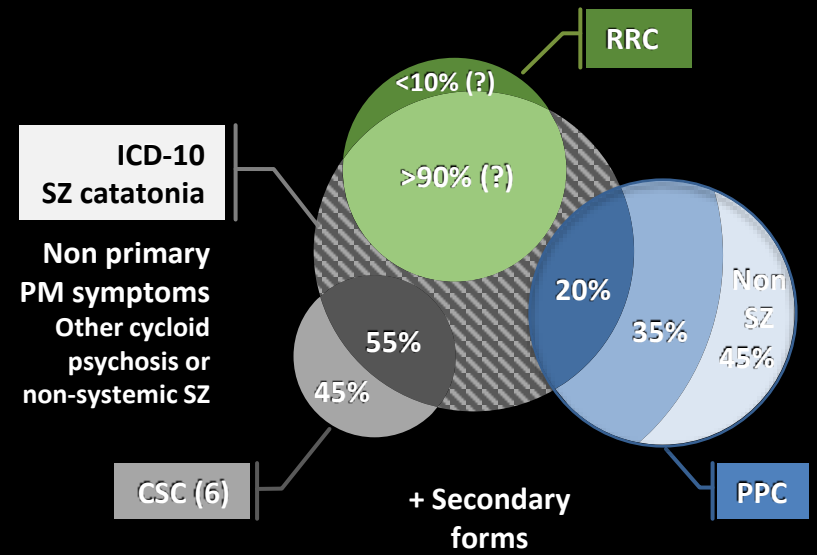
Foucher et al. 2022

Course: Not one but many catatonic phenotypes

Longitudinal + course (remitting *vs* progressive) heuristics



Relationship of 3 main PM phenotypes with ICD-10 schizophrenic catatonia

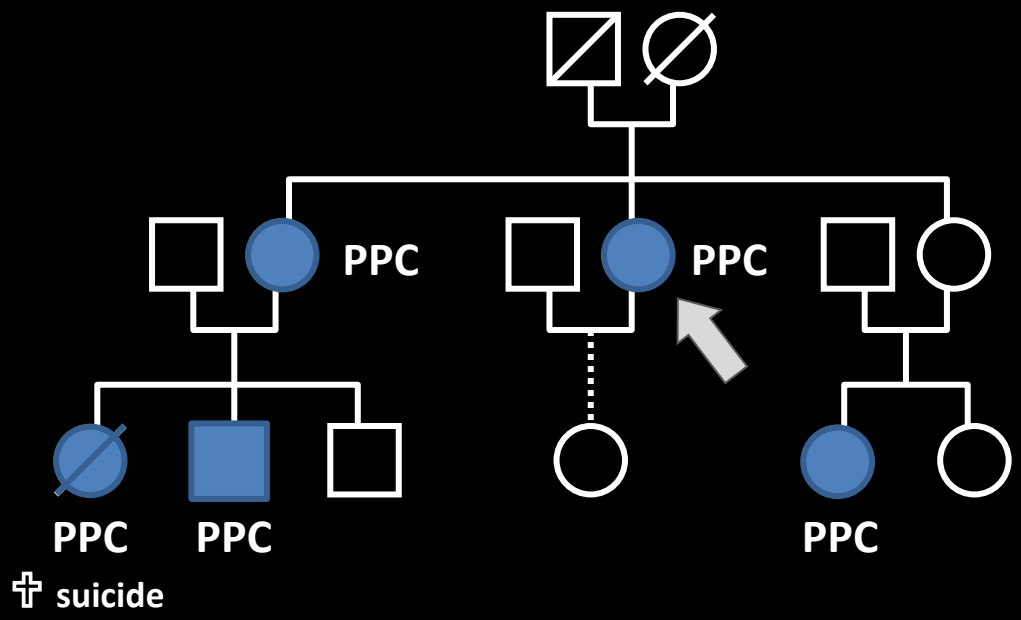


Foucher et al. 2022

PM phenotype: familial aggregation over resemblance

1942-68
"Aufteilung der endogenen Psychosen"

Karl Leonhard
(1904-1988)



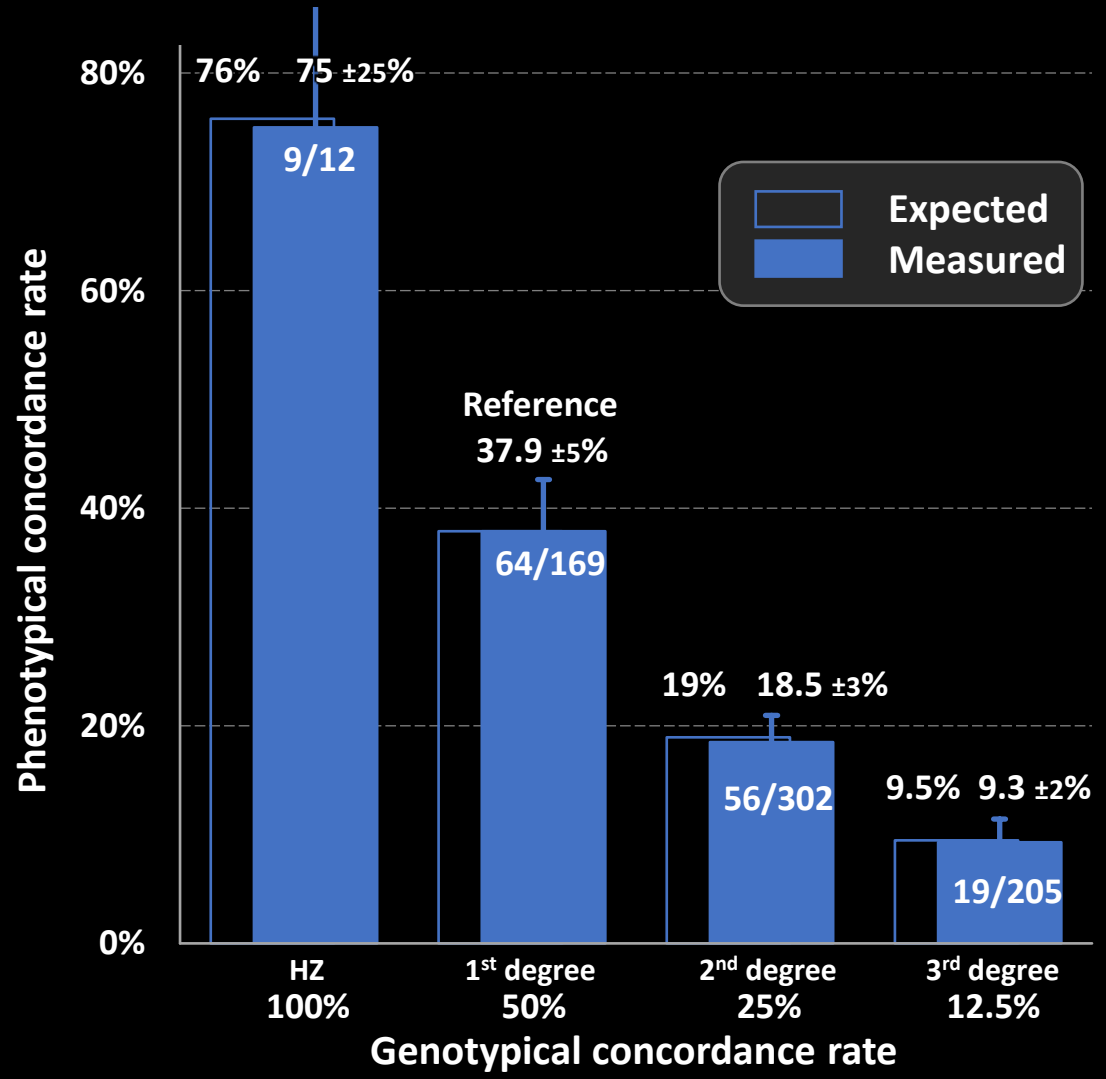
Help when saliant features are polymorphic

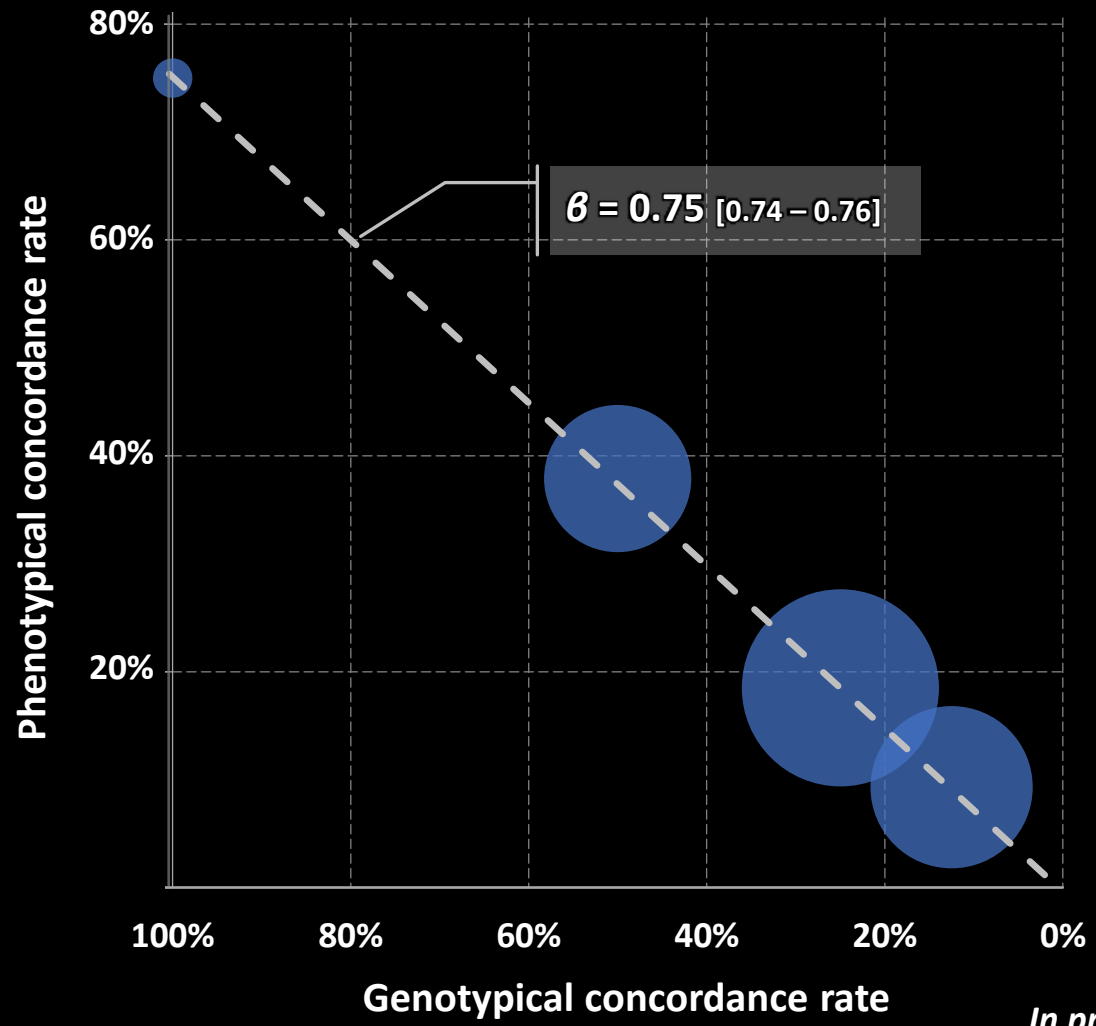
→ PPC has nothing to do with the mere repetition of ICD/DSM catatonic episodes

- **Coherence with current knowledge**
  - System neuroscience and symptom-complex
- **Longitudinal heuristic**
  - 1 patient = 1 phenotype (life-long stable)
  - Course (progressive / remitting)
- **Family aggregation heuristic**
  Same liability > resemblance
  - Multiplex family = 1 phenotype

Leonhard 1981

PPC is highly heritable – Mendelian heredity

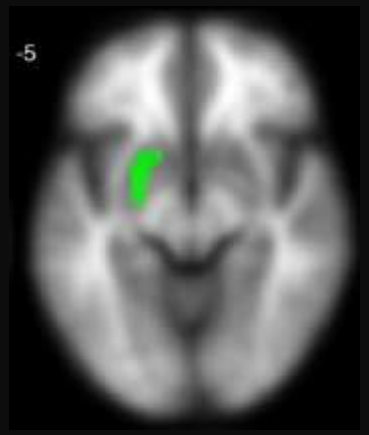




In preparation

Group study 1: PC as an independent phenotype

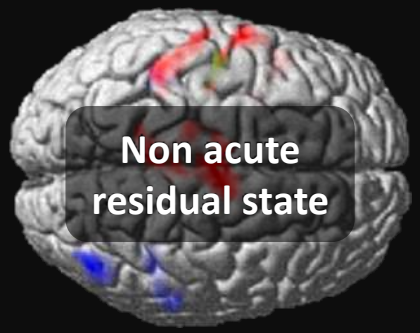
PPC | C | SZ

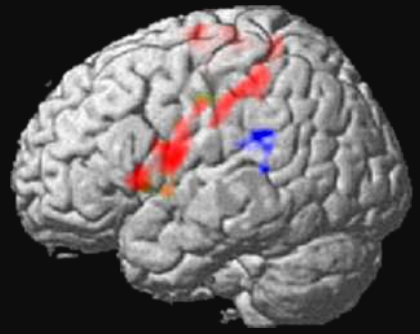


SZ vs. CTR :
⇗ rCBF L striatum & premotor Cx
Classical antipsychotics effect
No hypo DLPFCx ⇨ Cycloid psychoses

wkj

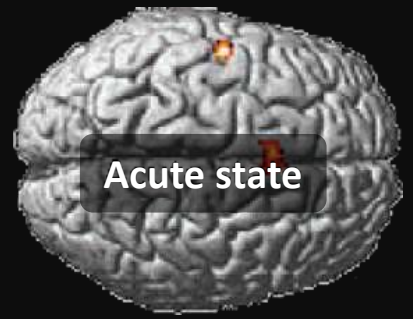
Double dissociation





PPC
Specific ⇗ rCBF L-PMC
Structure-function correspond.

Cataphasia
Specific ⇘ rCBF TPJ bilaterally
Correlation with TePEO-C
(r = - 0.68, p = 0.012)

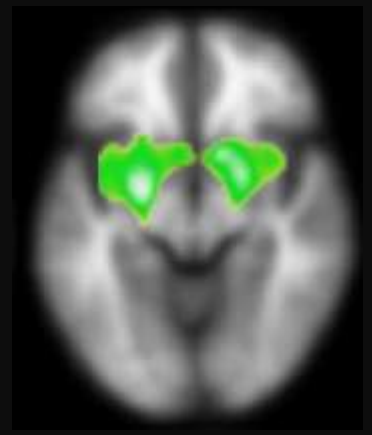


Walther et al. 2017

Foucher et al. 2018

Group study 2: replication

PPC C SZ



SZ vs. CTR :
⇗ rCBF L striatum & premotor Cx
Classical antipsychotics effect

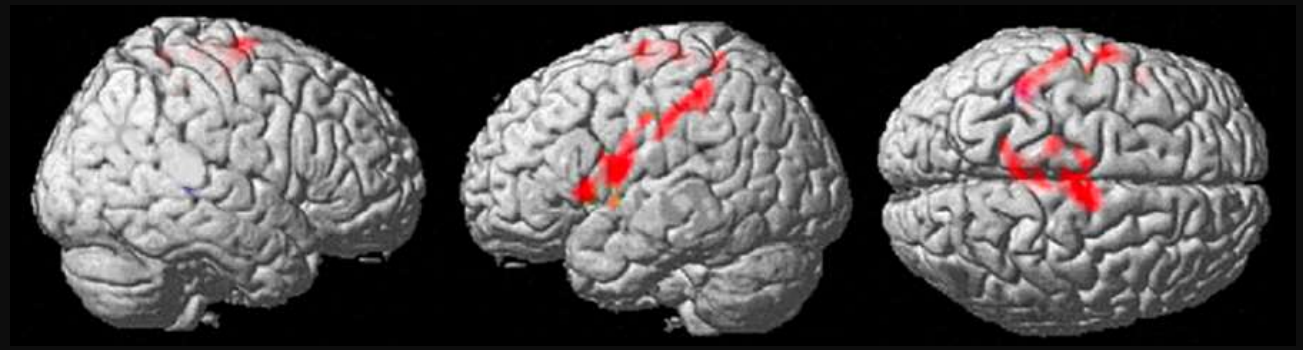
Multiple dissociations

wkl

total = 50 PC

n = 19

PPC
Specific ⇗ rCBF L-PMC



Foucher et al. 2018

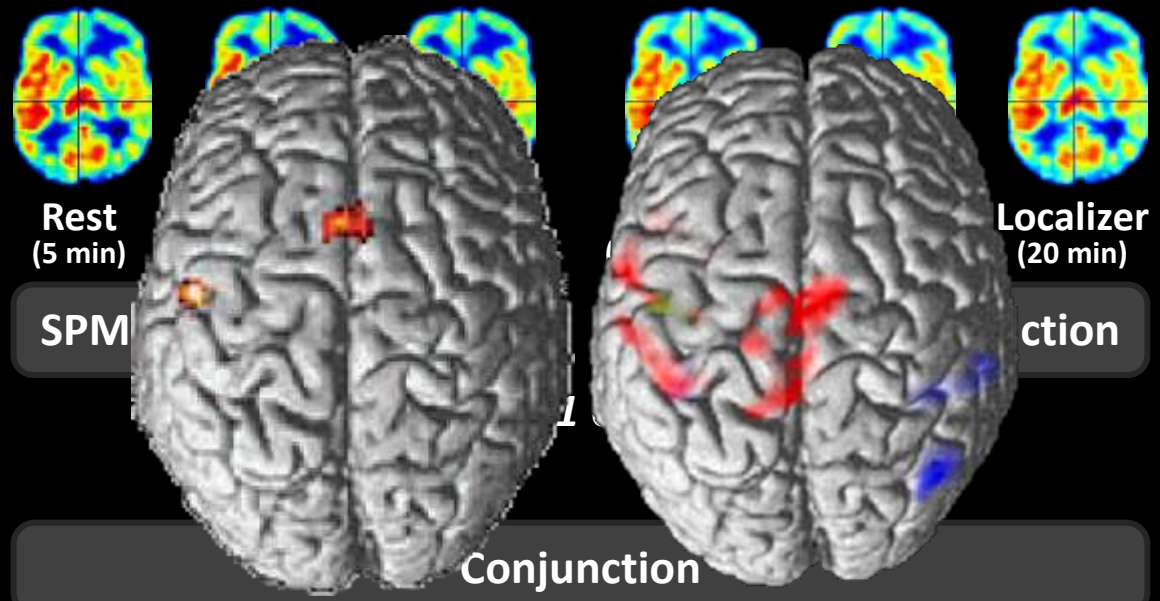
n = 31

Arcay et al. in prep

Premotor hyper-perfusion as biomarker study 1 & 2

Clément de Billy's presentation this morning

ASL/PMC-rCBF as a biomarker?



Walther et al. 2017

Foucher et al. 2018

At least 1 of 2 vx from previous studies: SMA and/or L-PMC

Results (z > 3)

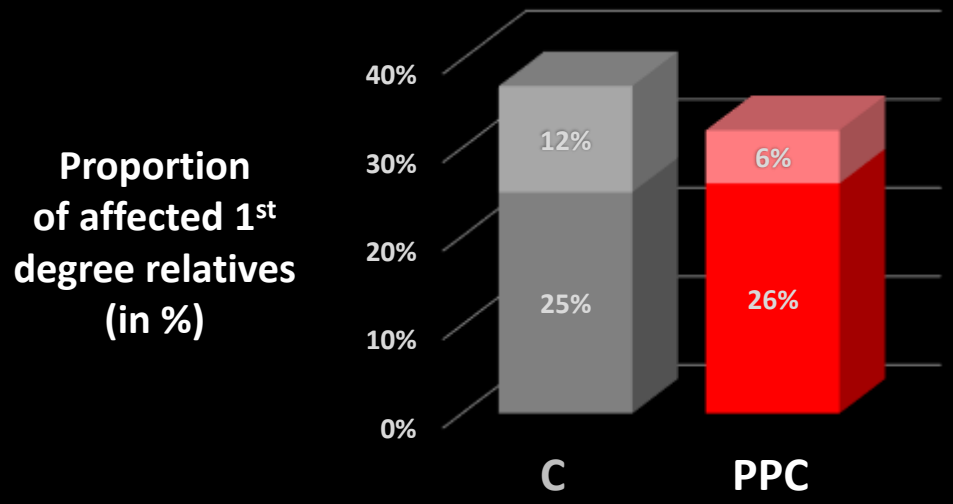
- **S1: RETONIC** (NCT03116425)
  - 3 MRI sessions
  - > 1 week apart
- **S2: Neurosplit'Z** (NCT03649581)
  - 2 MRI sessions
  - > 1 week apart

- **Bayesian update**
  Population n_{PPC} = 24, n_{nPPC} = 34
  - Sensitivity = 82%
  - Specificity = 95%
- **2nd study: uncertain diagnoses**
  In 2 cases → diag. correction

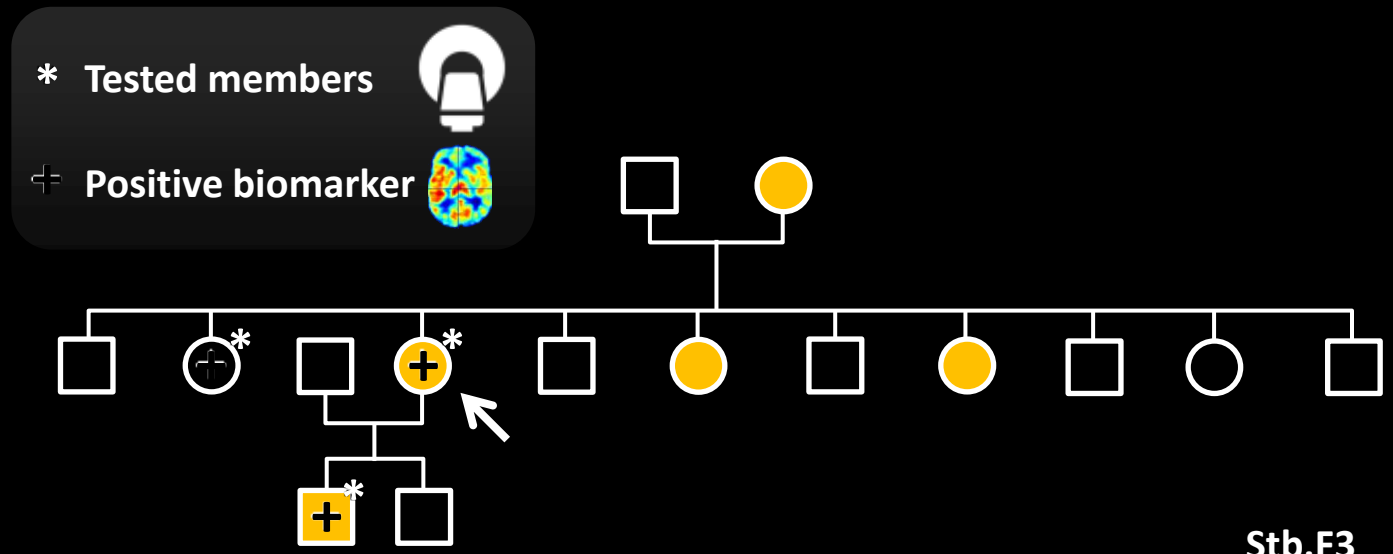
Foucher et al. 2000
de Billy master thesis
de Billy et al. in preparation

Does the biomarker work for PPC extended phenotype?

In multiplex families, affected members are more likely to share the same liability

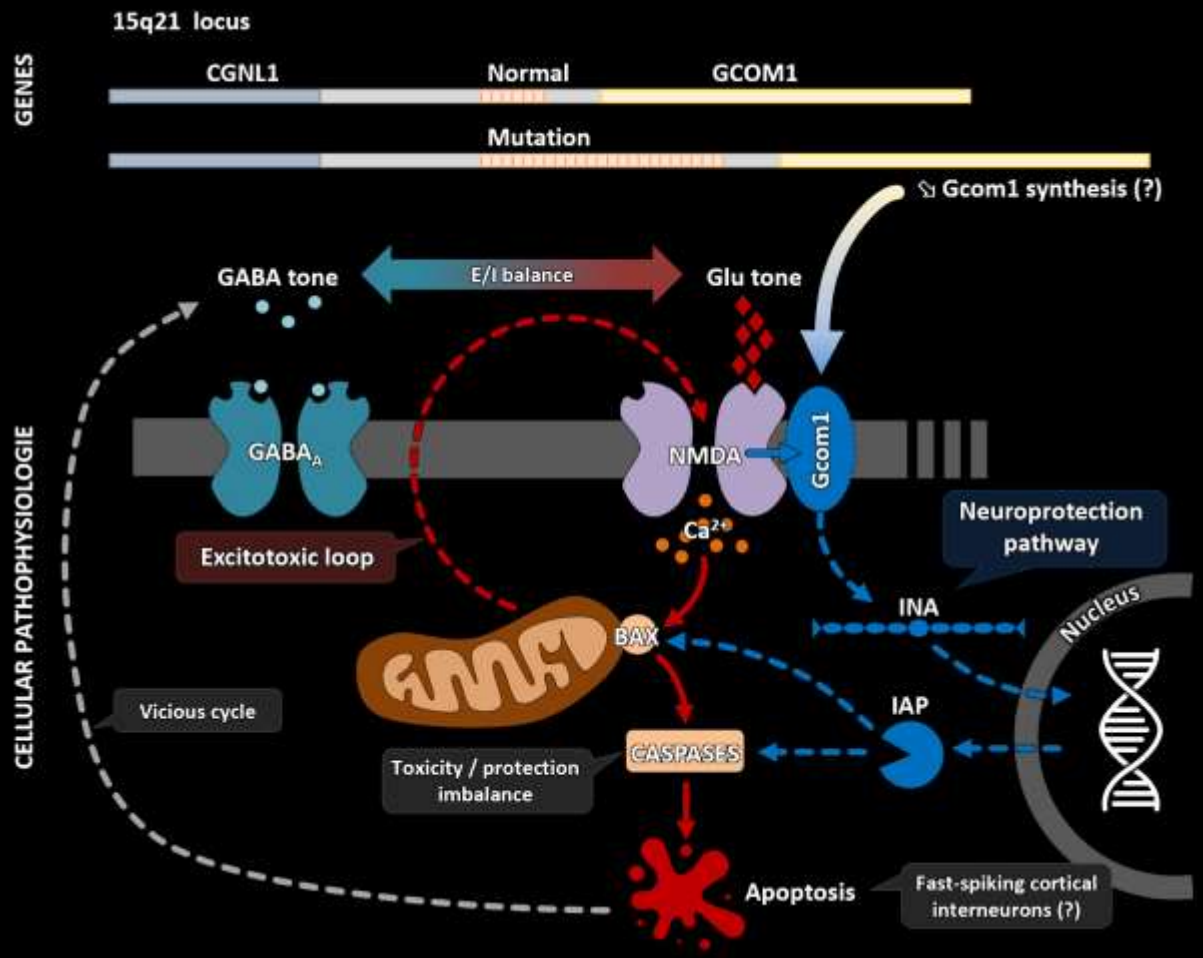


- Extended PPC phenotype
- Incomplete penetrance: could the biomarker help detecting sub-clinical carriers (extended phenotype)?



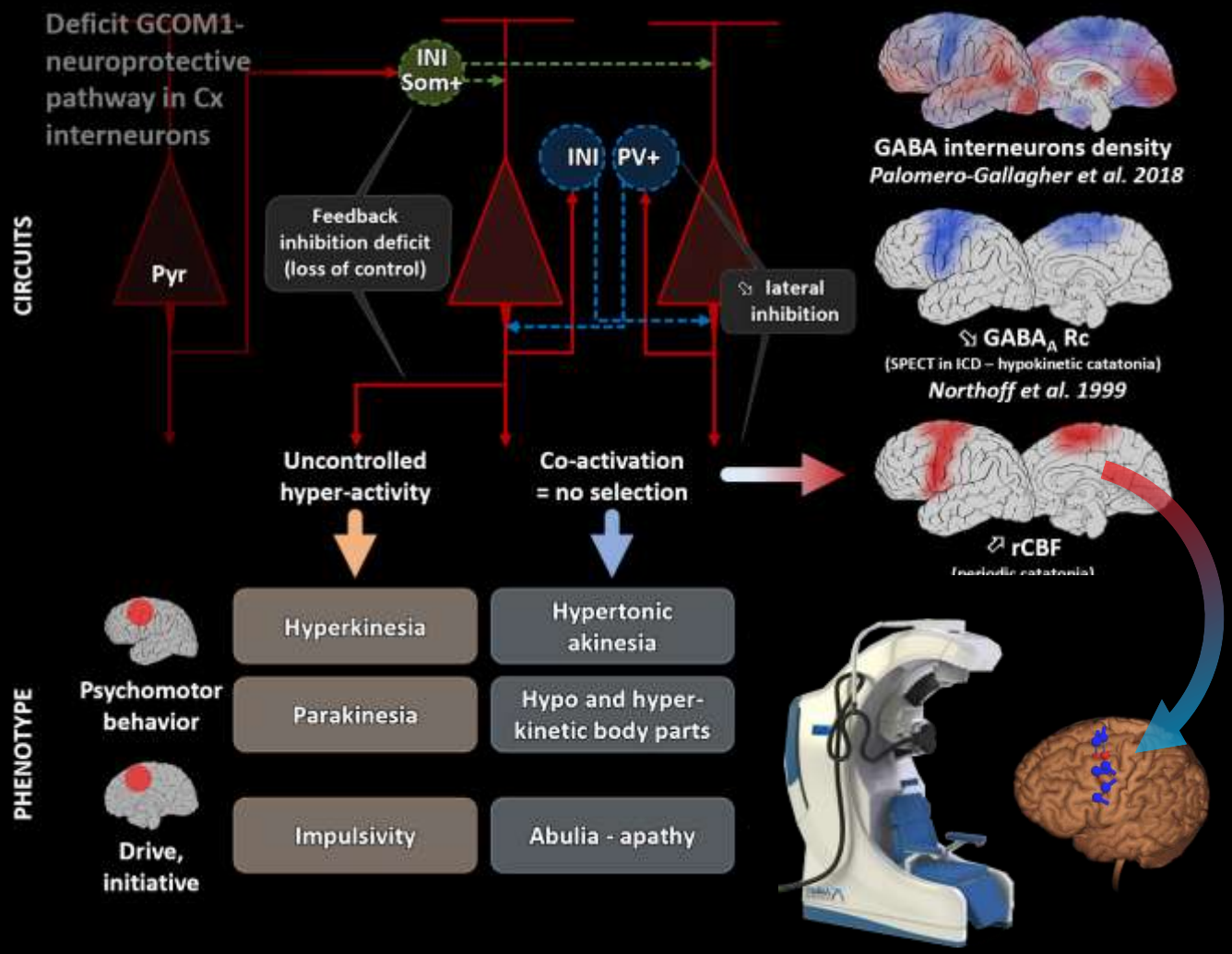
Stb.F3

Top-down etio-pathophysiological model of PPC



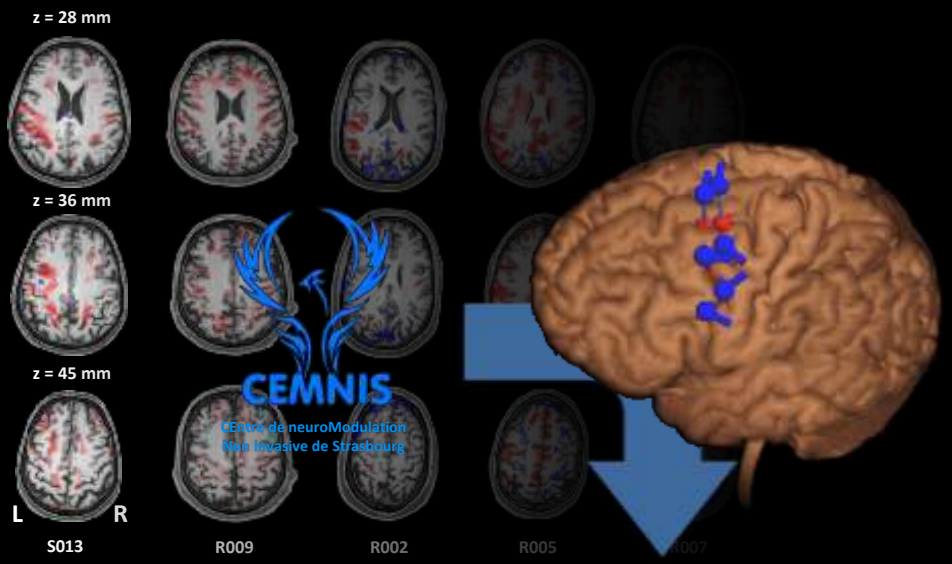
- PPC is a be-able phenotype
  - Reliable (κ = 0.93)
  - Life-long stable
  - Consistent in family (no cross liability)
- Top-down etio-pathophysiological model of PPC
  - ↘ GCOM1-neuroprotective pathway (½ - ⅔ of cases)
  - Excitotoxic – neuroprotection imbalance

Top-down etio-pathophysiological model of PPC



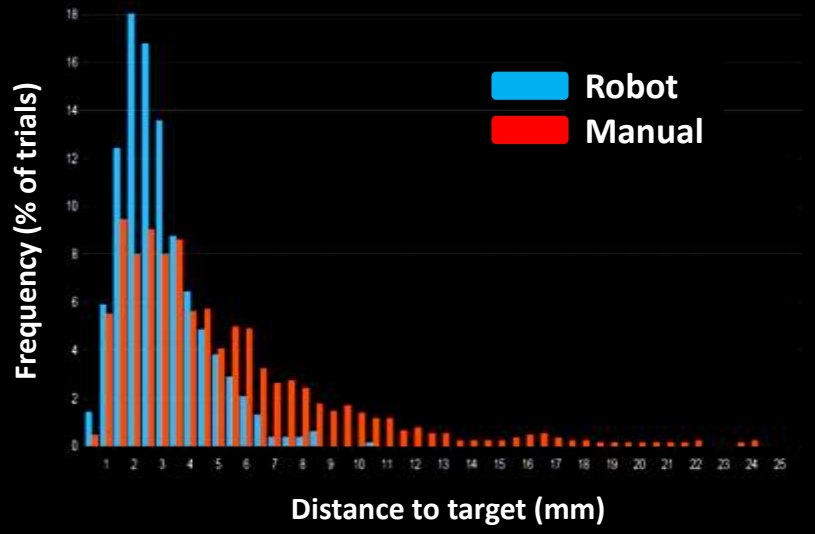
- **PPC is a be-able phenotype**
  - Reliable (κ = 0.93)
  - Life-long stable
  - Consistent in family (no cross liability)
- **Top-down etio-pathophysiological model of PPC**
  - ↘ GCOM1-neuroprotective pathway (½ - ⅔ of cases)
  - Excitotoxic – neuroprotection imbalance
  - Inhibition deficit +++ SMA/PMC
    ⇨ system neuroscience account (postural systems)
- **Therapeutic perspective**
  - We know who: PPC
  - We know where: SMA/PMC (even personalized)
  - We know how: increase intracortical inhibition

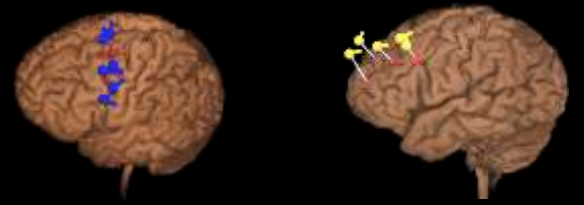
Translation: reinforcing SMA/PMC inhibition with rTMS



Methodological development: accelerated neuromodulation protocols of extended and complex regions

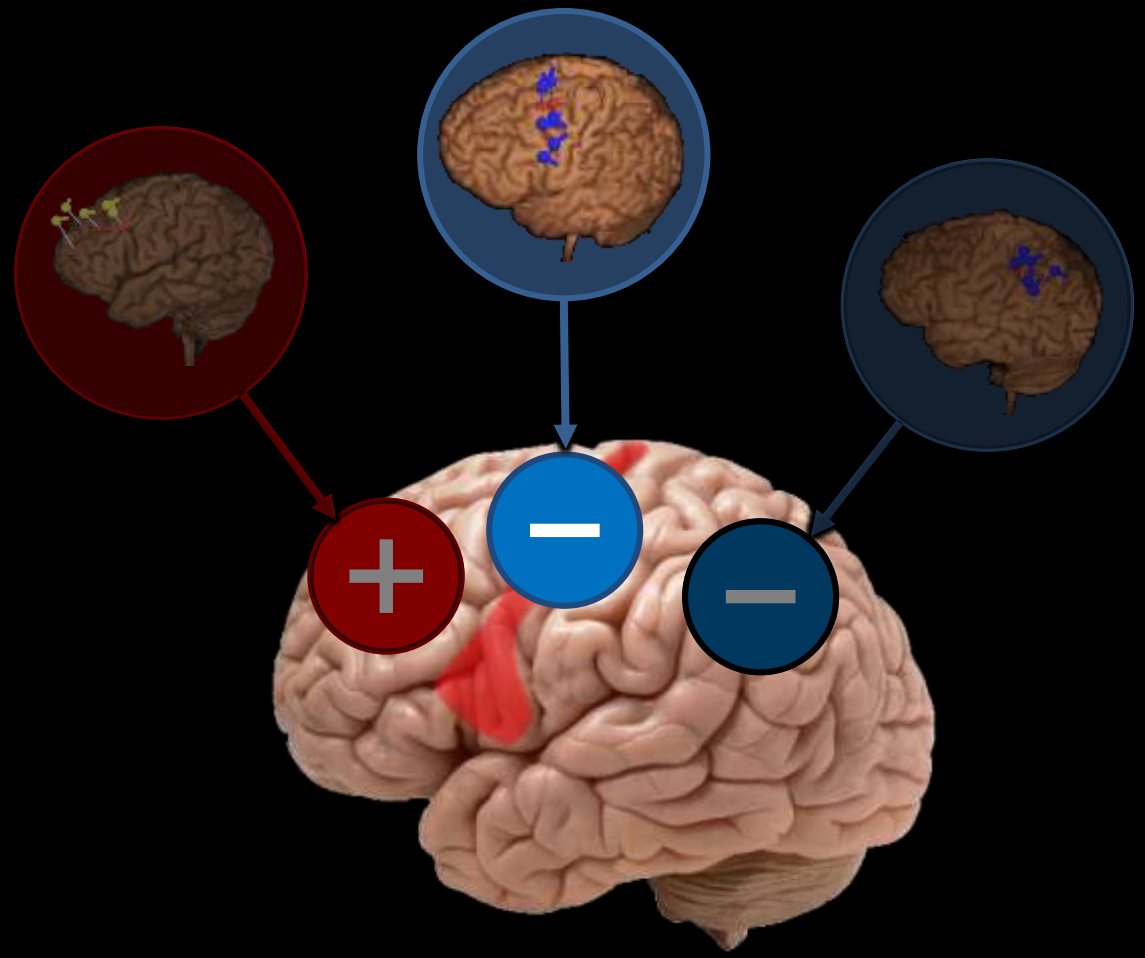
- **Neuro-navigated robotic device**
  - Fast, non tiering procedure
  - Comfortable for the patients
  - Outperform human precision
- **Accelerated protocols:**
  - Multiple targets (4-5)/ sess.
  - Theta burst : 40 à 200 sec/target (cTB$^{\ominus}$, iTB$^{\oplus}$)
  - 4 sessions /d (> 1h apart)
  - 5 days in a row





5 targets x 4 sess. x 5d
= 100 sessions in a week !

Proof of concept intervention study

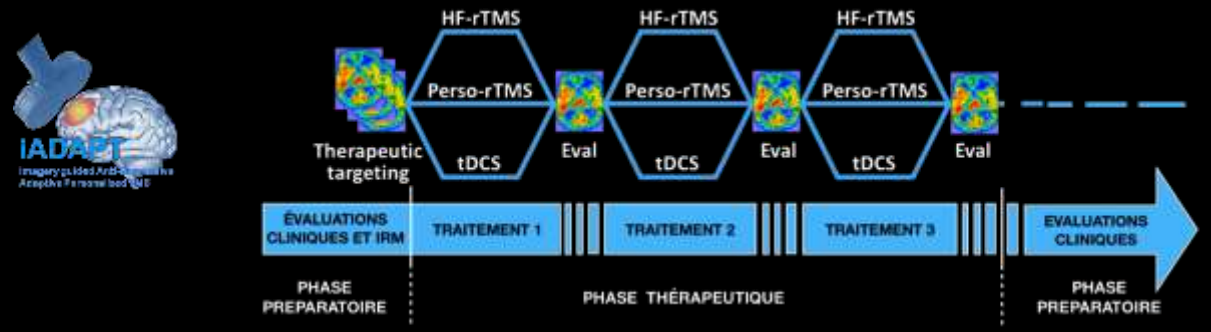


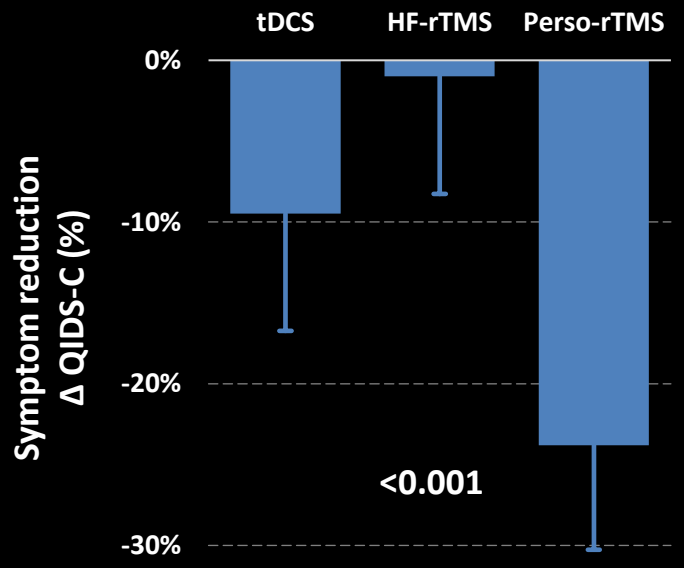
- **Patients all 3 protocols** (randomize order)
  - PMC inhibition
  - vs DLPFC stimulation (active comparator), and parietal inhibition (CTR)
- **Preliminary results (n = 10)**
  - ↘ deficit syndrome (+++ apathy) = negative symptoms dimension
  - Specific for SMA/PMC inhibition
  - Enduring
  - 6 patients under maintenance TTT (0.3 – 2/M)
    Astonishing long-term outcomes!

Reinforcing SMA/PMC inhibition
Improves core residual Σ

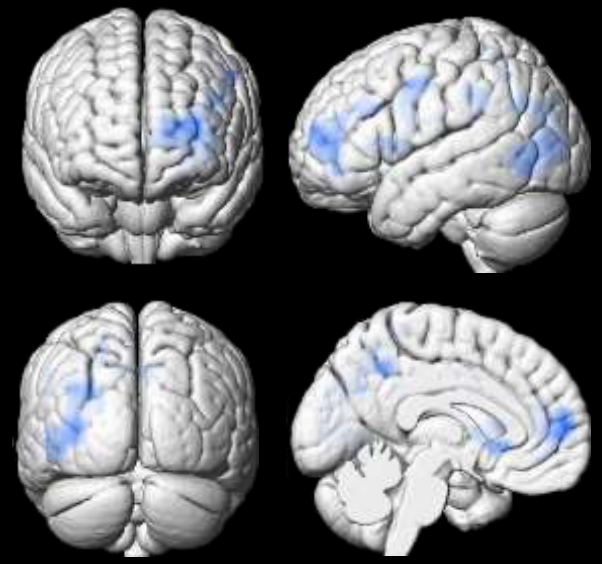
Is this just a matter of correcting brain anomalies?

Ludovic Dormegny-Jeanjean's presentation this morning





Dormegny-Jeanjean et al. in preparation



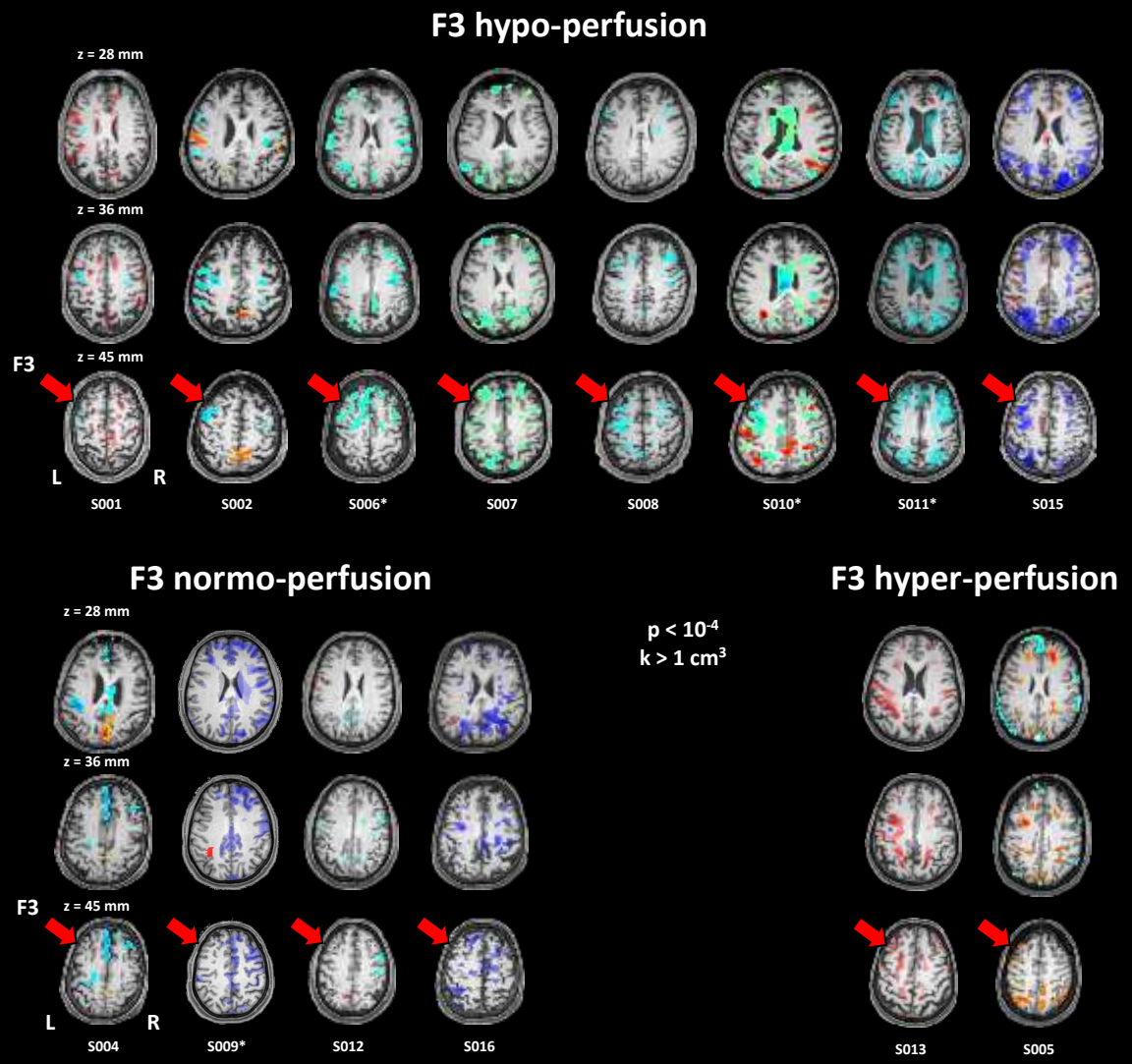
rCBF reduction (Δ post-pre)

$p < 10^{-6}$, $k > 200\ mm^3$; Only for perso-rTMS

- **Cross-over** (randomize order)
  - tDCS (anodal F3, 2 mA, 20 min, × 20)
  - HF-rTMS (F3, 120%, 10 Hz, 3600 p, × 20)
  - Perso-rTMS: adapting where and how (120%, 1 Hz - 1200 p and/or 10 Hz - 3600 p, × 20)
- **Symptom improvement and rCBF changes only in perso-rTMS**

Is this just a matter of correcting brain anomalies?

Ludovic Dormegny-Jeanjean's presentation this morning

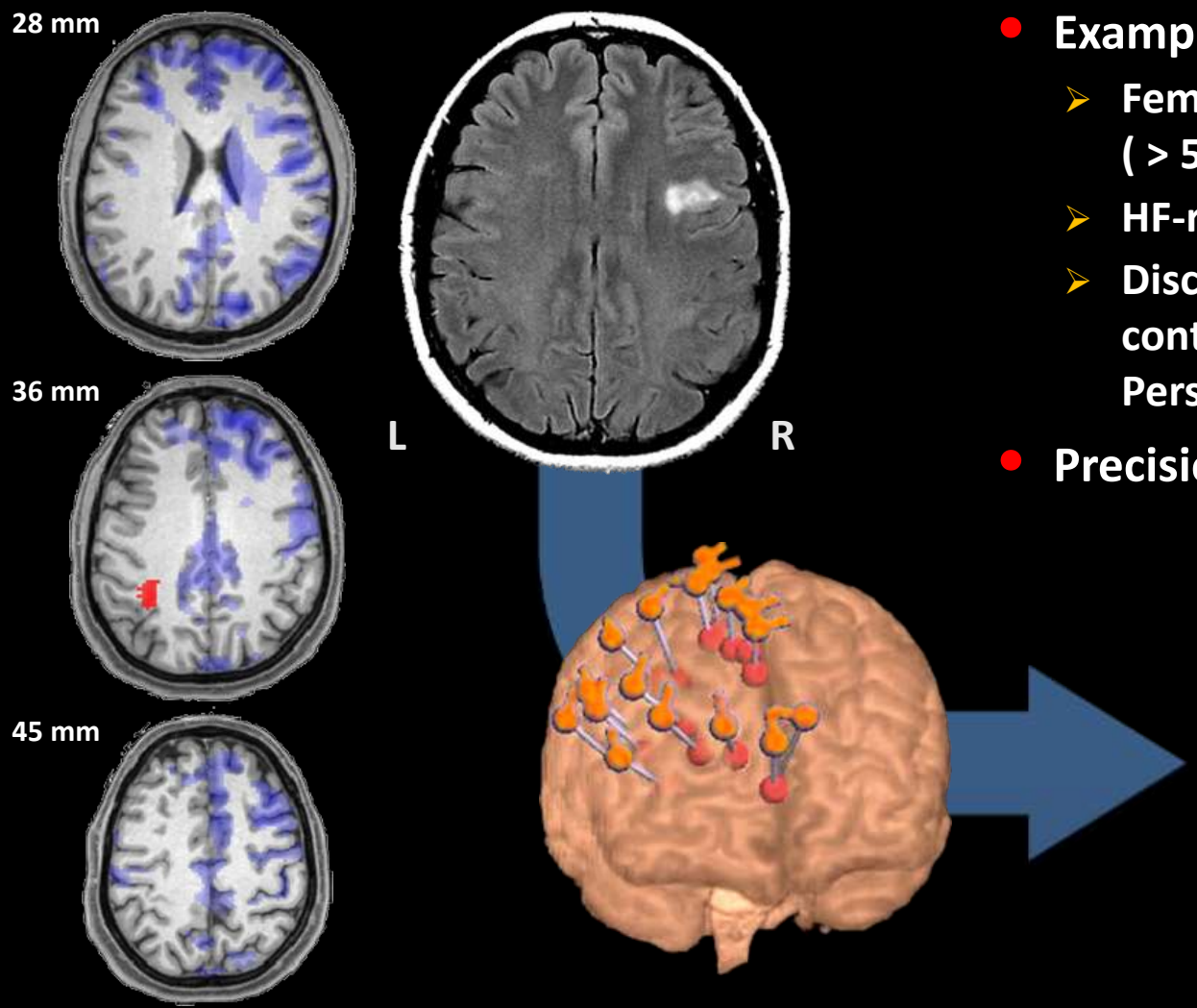


- Cross-over (randomize order)
  - tDCS (anodal F3, 2 mA, 20 min, × 20)
  - HF-rTMS (F3, 120%, 10 Hz, 3600 p, × 20)
  - Perso-rTMS: adapting where and how (120%, 1 Hz - 1200 p and/or 10 Hz - 3600 p, × 20)
- Symptom improvement and rCBF changes only in perso-rTMS
- Why not in HF-rTMS?
  - 55% with L-DLPF hypo-perfusions
  - 30% without significant L-DLPF changes
  - and ... 15% with L-DLPF <u>hyper</u>-perfusion
- Not one but many TRD syndrome or phenotypes?

Most impressive results on secondary TRD

Ludovic Dormegny-Jeanjean's presentation this morning

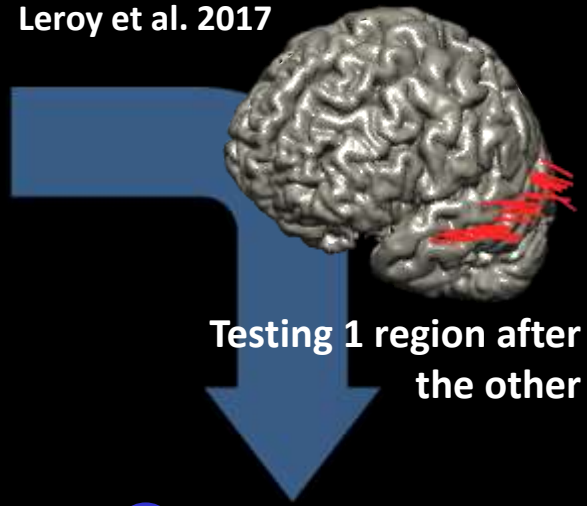
$p < 10^{-4}$
$k > 1\ cm^3$



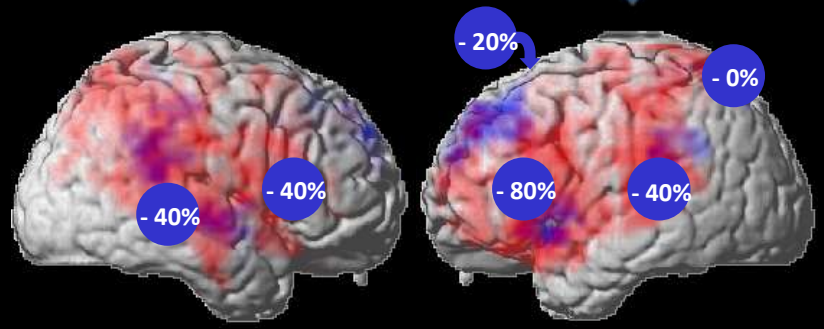
- **Example**
  - Female, 20 years old with TR double depression (> 5 years)
  - HF-rTMS ineffective
  - Discovery of a L-frontal focal dysplasia with contralateral hypoactivation – no EEG anomalies
    Perso-rTMS effective ⇨ relapses if stops (1/15 d)
- **Precision *vs* personalized treatment?**

Better with a little understanding

Kappa vx
SPM = 0.12 *vs* ICA = 0.6
Leroy et al. 2017



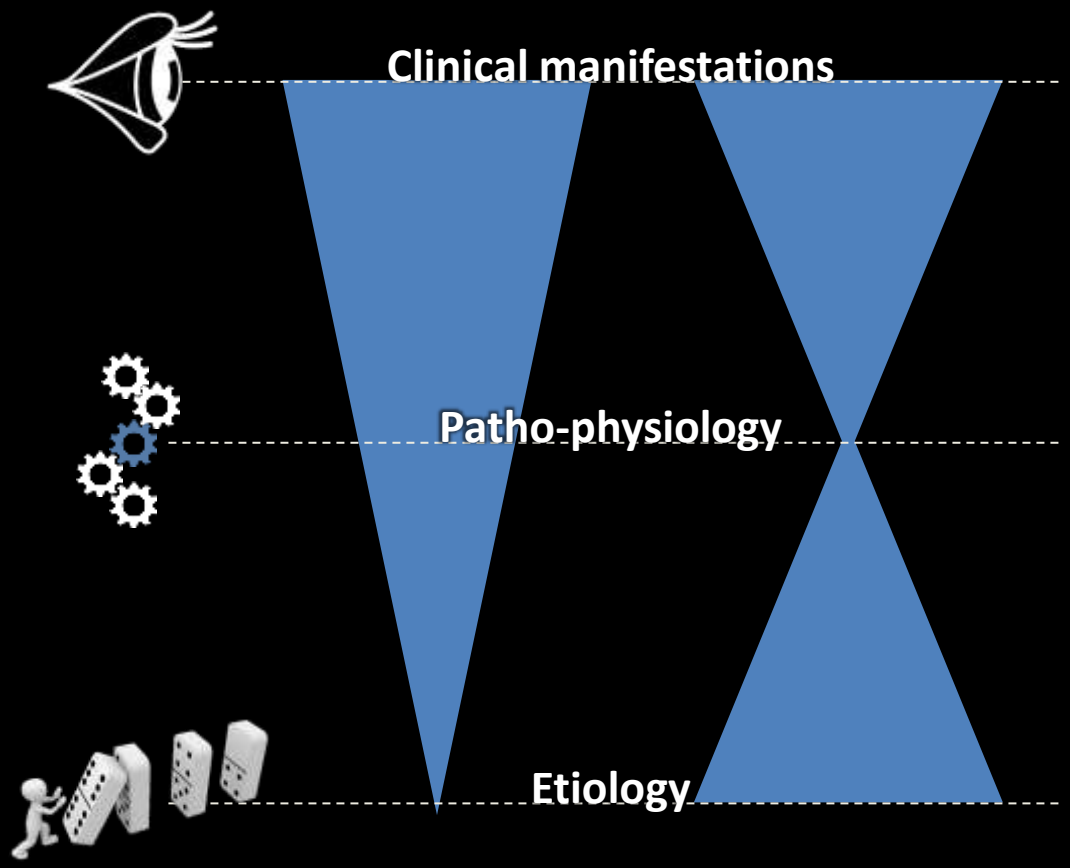
Testing 1 region after the other



Hyperactive during AVH
Disconnected during AVH ($p < 0.001$)

- There are (too) many possible targets
  - Trial and error (hallucinations)
    ⇨ TRD guidelines
  - Personalization is not enough

Better with a little understanding



- There are (too) many possible targets
  - Trial and error (hallucinations)
    ⇨ TRD guidelines
  - Personalization is not enough
- We need to understand the pathophysiology behind the symptoms
  - Precision medicine = expectation about most effective intervention (who, where and how)
  - Personalization should only be the final adjustment
- NIBS:
  - Fast interventional test → Fast translation
  - Treatment or rare (orphan) syndromes/diseases

Remerciements :

Fabrice Berna, Clément de Billy, Olivier Mainberger, Ludovic Jenajean, Alexandre Obrecht, Julie Clauss, Benoit Schorr, Pierre Vidailhet, Sébastien Weibel, Marie-Agathe Zimmerman, Gilles Bertschy
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Julien Elowe

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Pr Gerald Stöber†, Dr Julian Roth, Dr Micha Gawlik

Univ. Dresde
Pr Burkhard Jabs, Pr Bruno Pfühlmann

Univ. Berne
Pr Sebastian Walther, Pr Werner Strick

Univ. Mannheim – Heidelberg (ZI)
Dr Andreas Bartsch, Dr Dusan Hirjak, Pr Christian Wolf

Thomas Ban

"By 1987, the time of the postulation of a "clinical prerequisite" for rendering findings in biological research in psychiatry interpretable, psychopathology and psychiatric nosology became forgotten languages".

Thank you for your attention

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