

THE FUTURE OF IMMUNO- PSYCHIATRY

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CAPRI symposium workshop

07-02-2023



Immuno-NeuroPsychiatry
ECNP Network

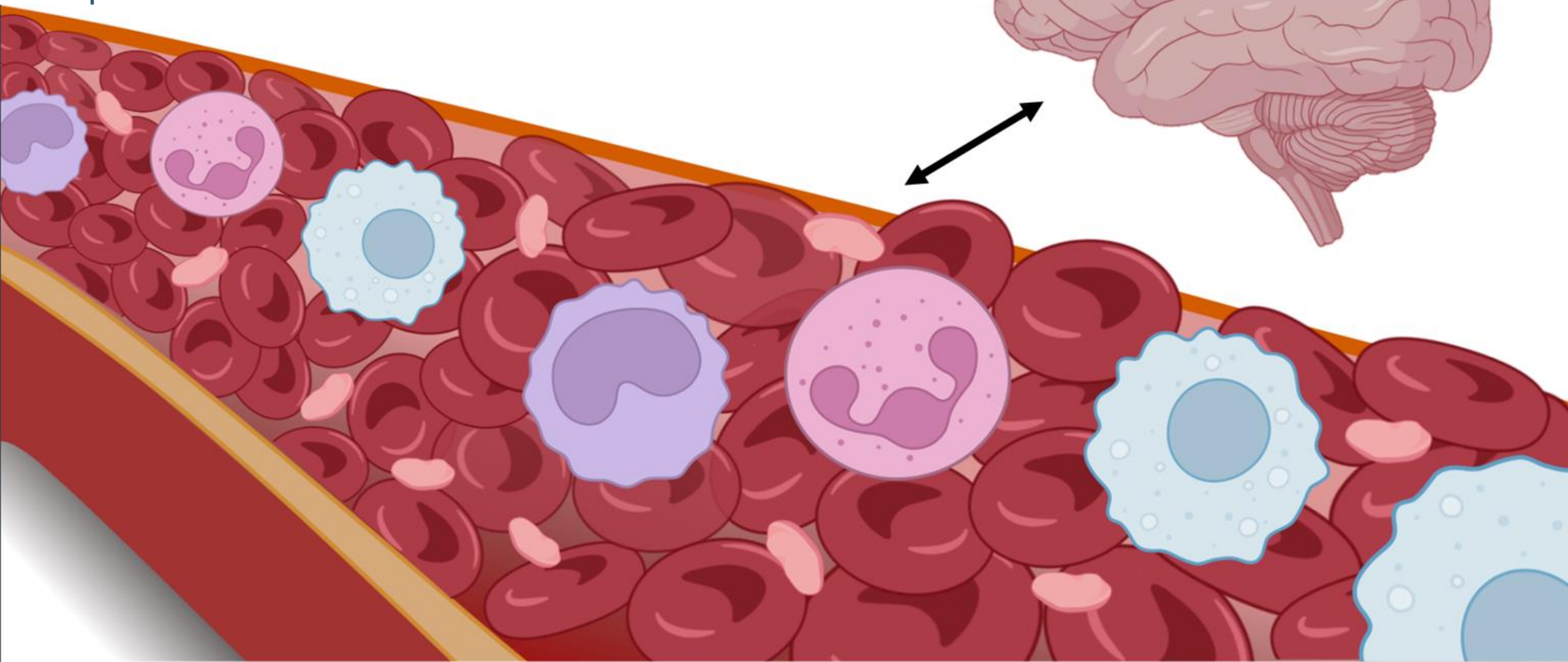
Immunopsychiatrie?

Ga naar: <https://www.menti.com/albdo1zidunx>

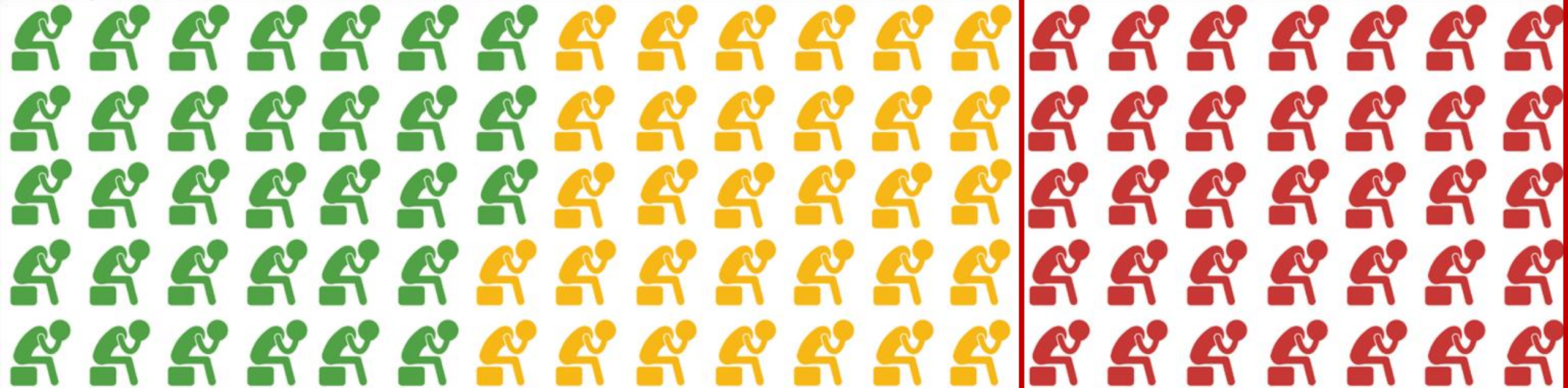
Of scan:

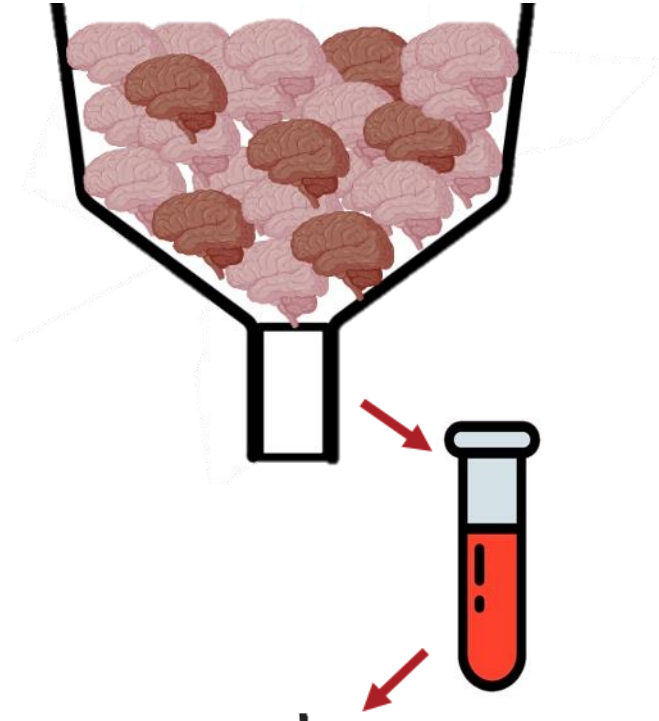


Immunopsychiatrie



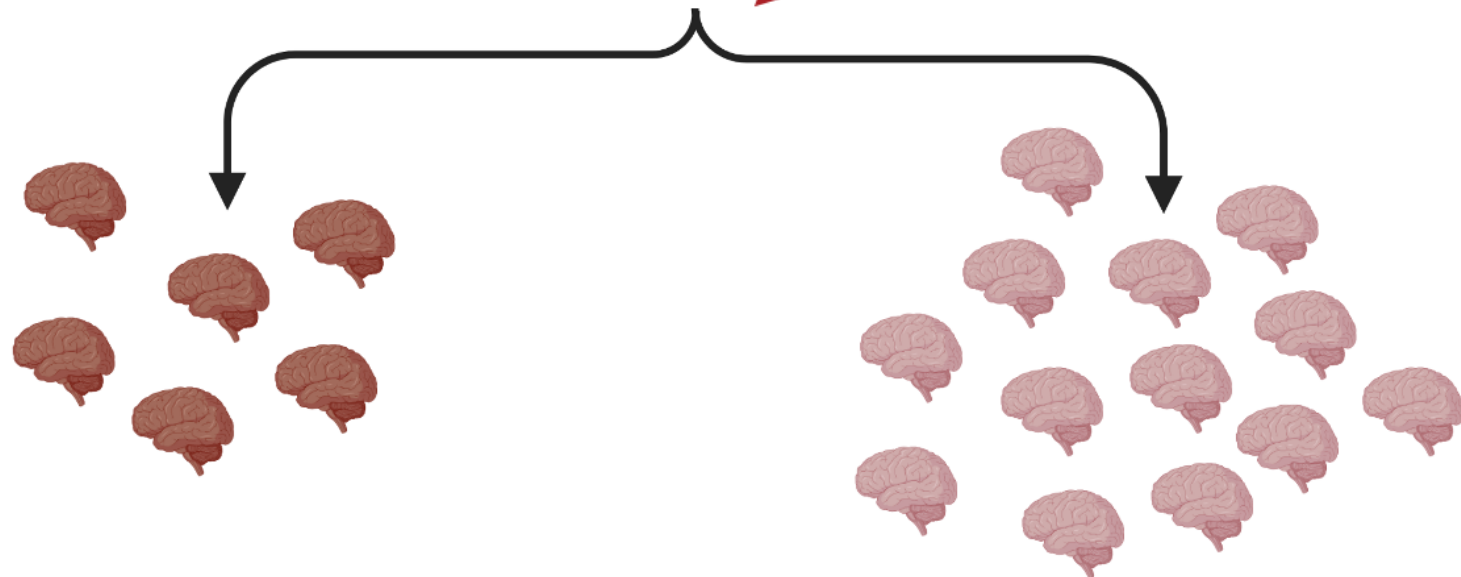
Depressie





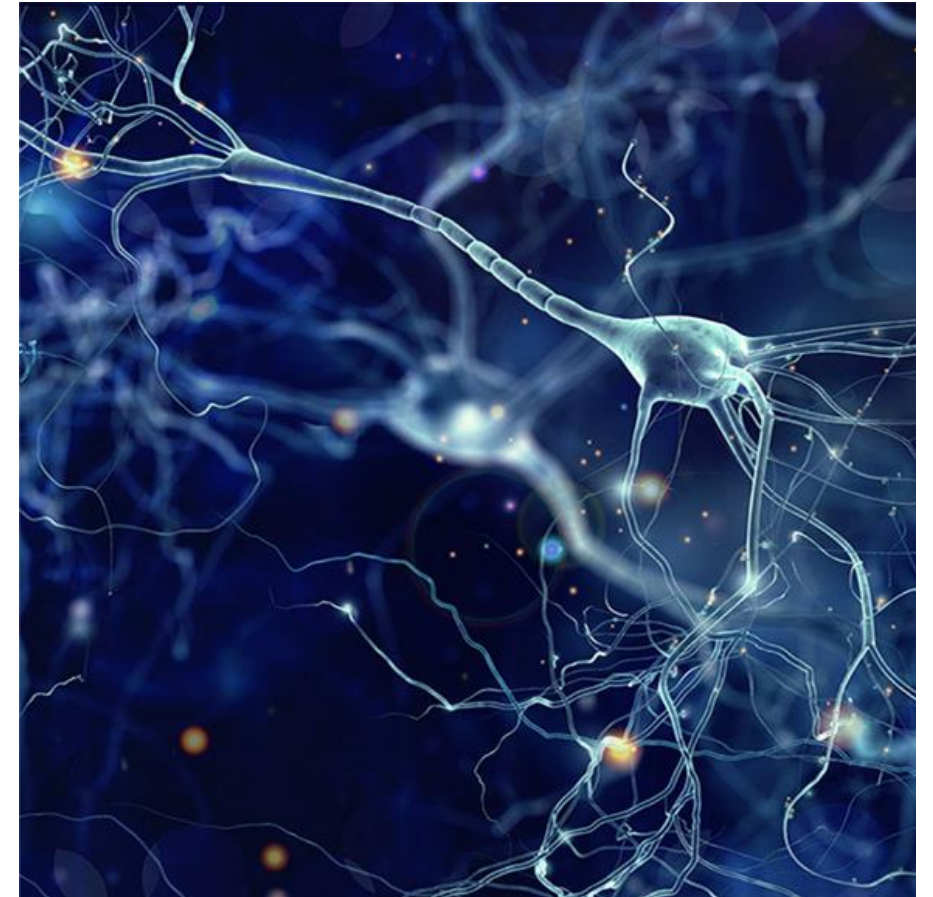
Overactief immuunsysteem

- > Ernstigere depressies
- > Minder goed behandelbaar



OUTLINE

1. PNI to IP
2. 3 critical milestones
3. Cui bono?
4. Innovation at SINAPS
5. COVID-19 as catalyst



PSYCHONEUROIMMUNOLOGY

TO

IMMUNOPSYCHIATRY

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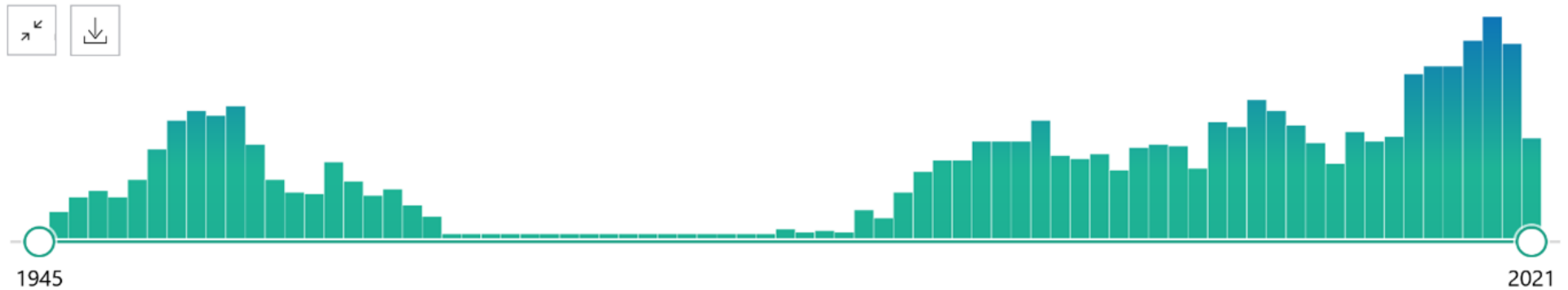
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“psychoneuroimmunology”

RESULTS BY YEAR

2,776 results



RESULTS BY YEAR

107 results



“immunopsychiatry”

The promise of immunopsychiatry

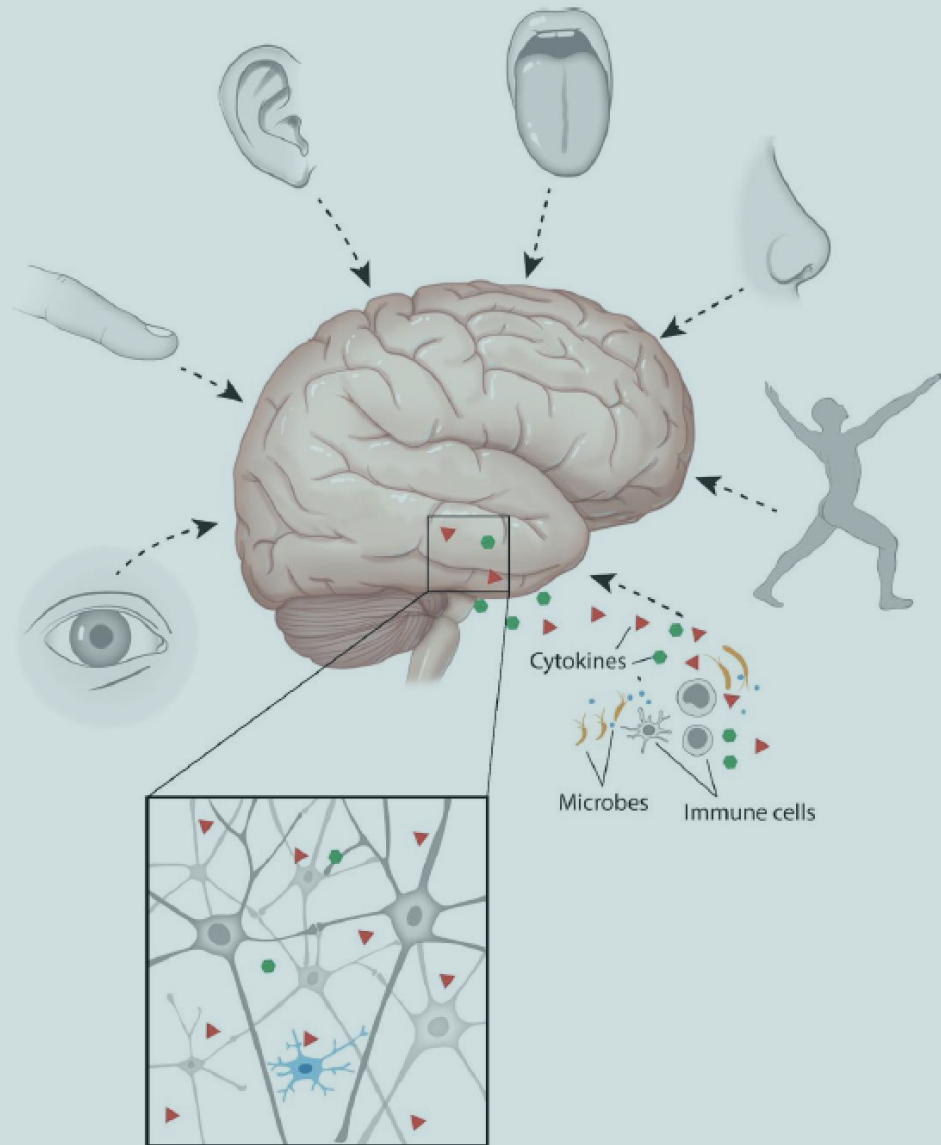
Important progress has been made in the last decade

IP has the potential to become a clinically relevant specialty area of psychiatry

Why is IP still considered a “niche” area with limited impact?



The immune system is now recognized as the « seventh sense » of the brain



The immune system detects microbes and stress, and communicates with the brain

THREE CRITICAL MILESTONES TOWARDS CLINICAL INNOVATION



3 critical milestones

- (1) a clear definition of patients who fall within the immunopsychiatric continuum;
- (2) demonstration of well-defined clinical benefit and incorporation in clinical guidelines;
- (3) convergence with other paradigms in biological psychiatry.



CUI BONO?

THE IMMUNOPSYCHIATRIC CONTINUUM

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Auto-immune encephalitis

Retrospective study of 111 patients with pure psychotic disorder and plasma Auto-AB against NMDA-R

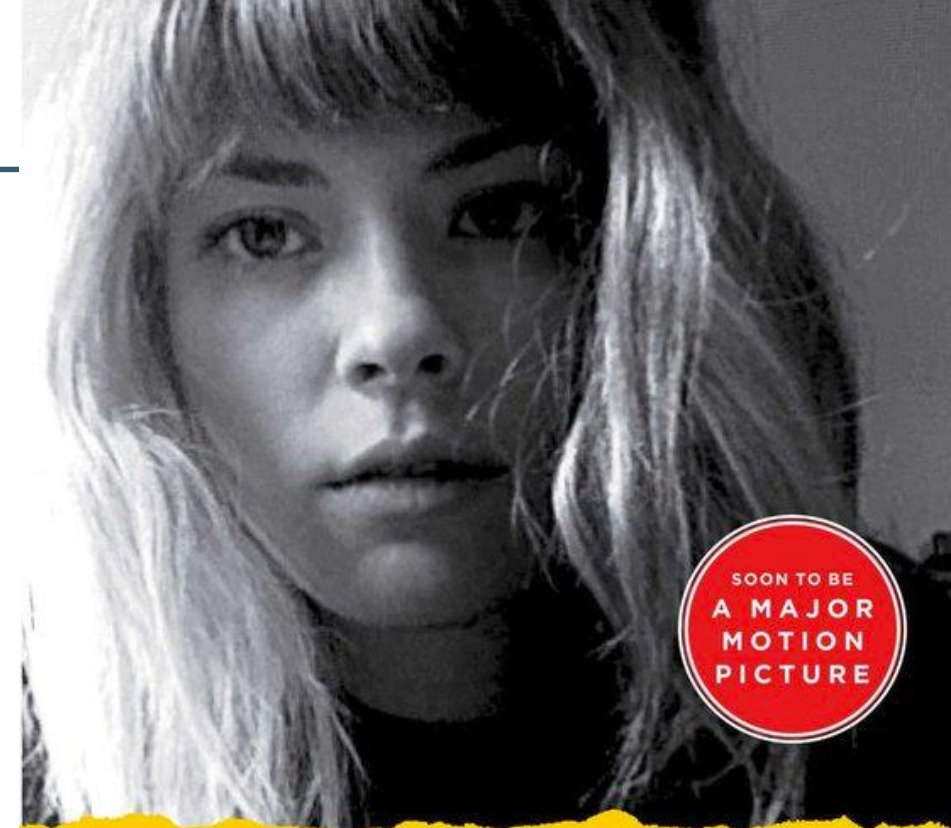
40%

initially hospitalized in psychiatry

No specific psychiatric symptoms :
mood, paranoid ideas, hallucinations

71%

of neurological subtle **symptoms**
Migraines, confusion, amnesia, epilepsy, paresthesia,
abnormal movements, dysarthria



#1 NEW YORK TIMES BESTSELLER

"Stunningly brave . . . an unexpected gift of a book from one of America's most courageous young journalists." —NPR

BRAIN ON FIRE

— *My Month of Madness* —

SUSANNAH CAHALAN

WITH A NEW AFTERWORD



Dualistic dichotomy

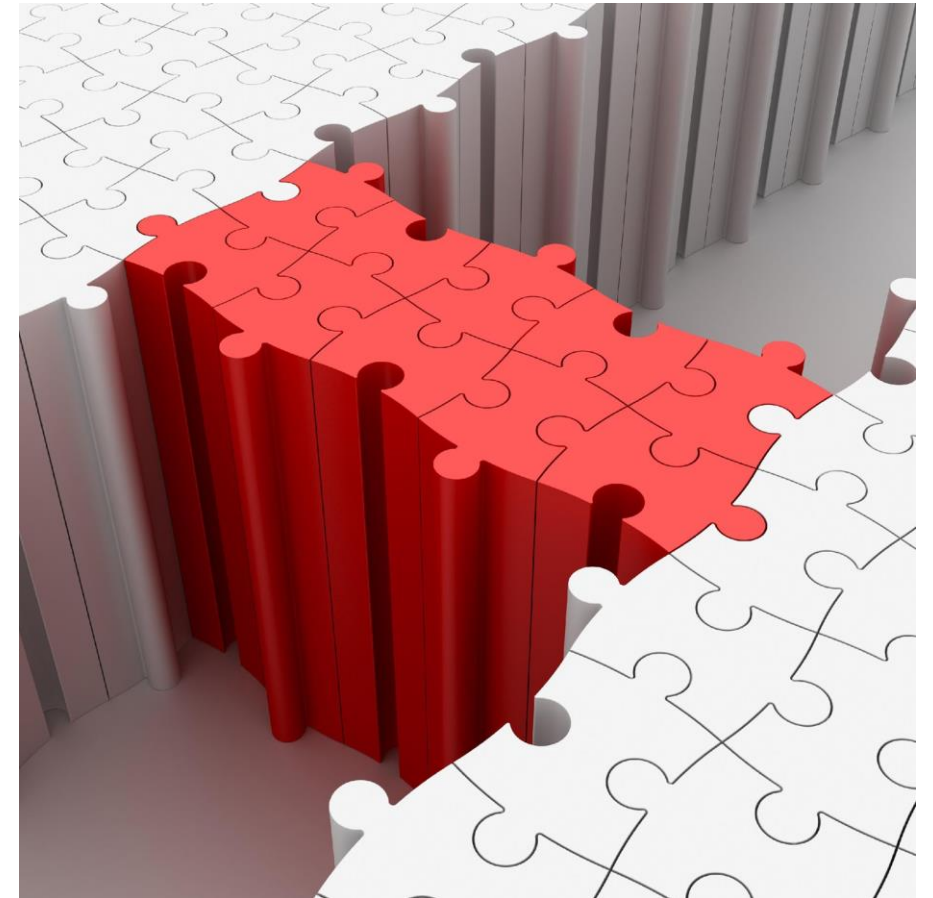
“Organic” vs. “primary” psychiatric syndromes

Psychiatrists vs other medical specialities

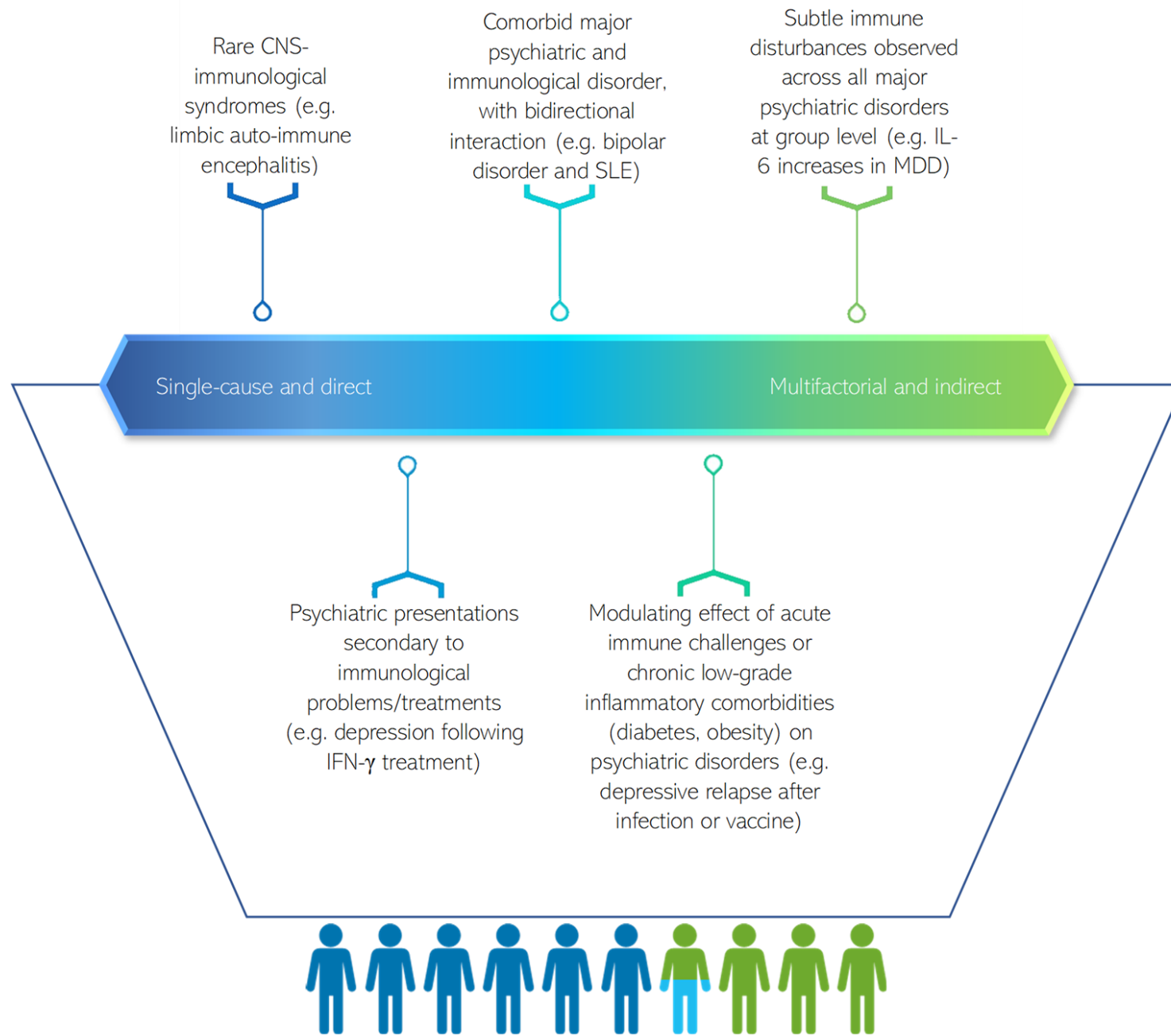
Not enough education, experience, attention

Not enough clinical guidelines

□ **under diagnosis & under treatment**



The immunopsychiatric continuum



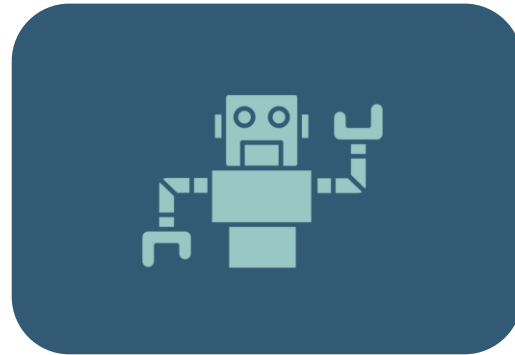
INNOVATION @SINAPS



INNOVATION @SINAPS



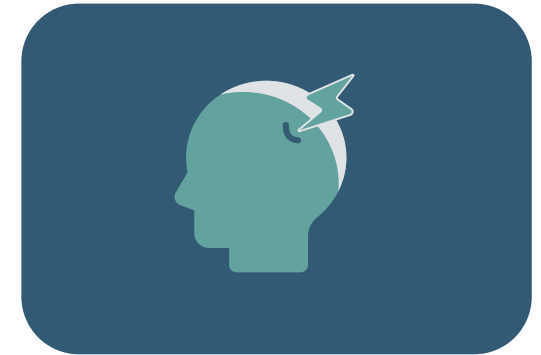
Meta/mega-analyse



Machine Learning



Predictive
biomarkers



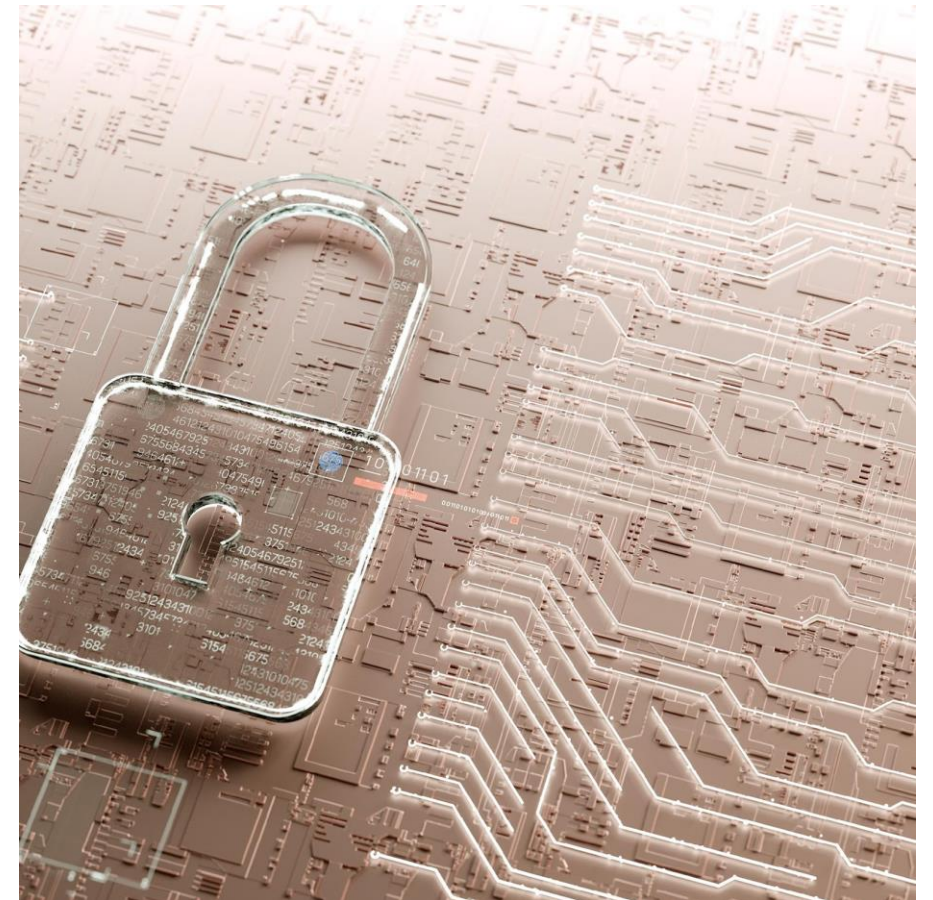
Stratified RCT
designs

3 critical milestones

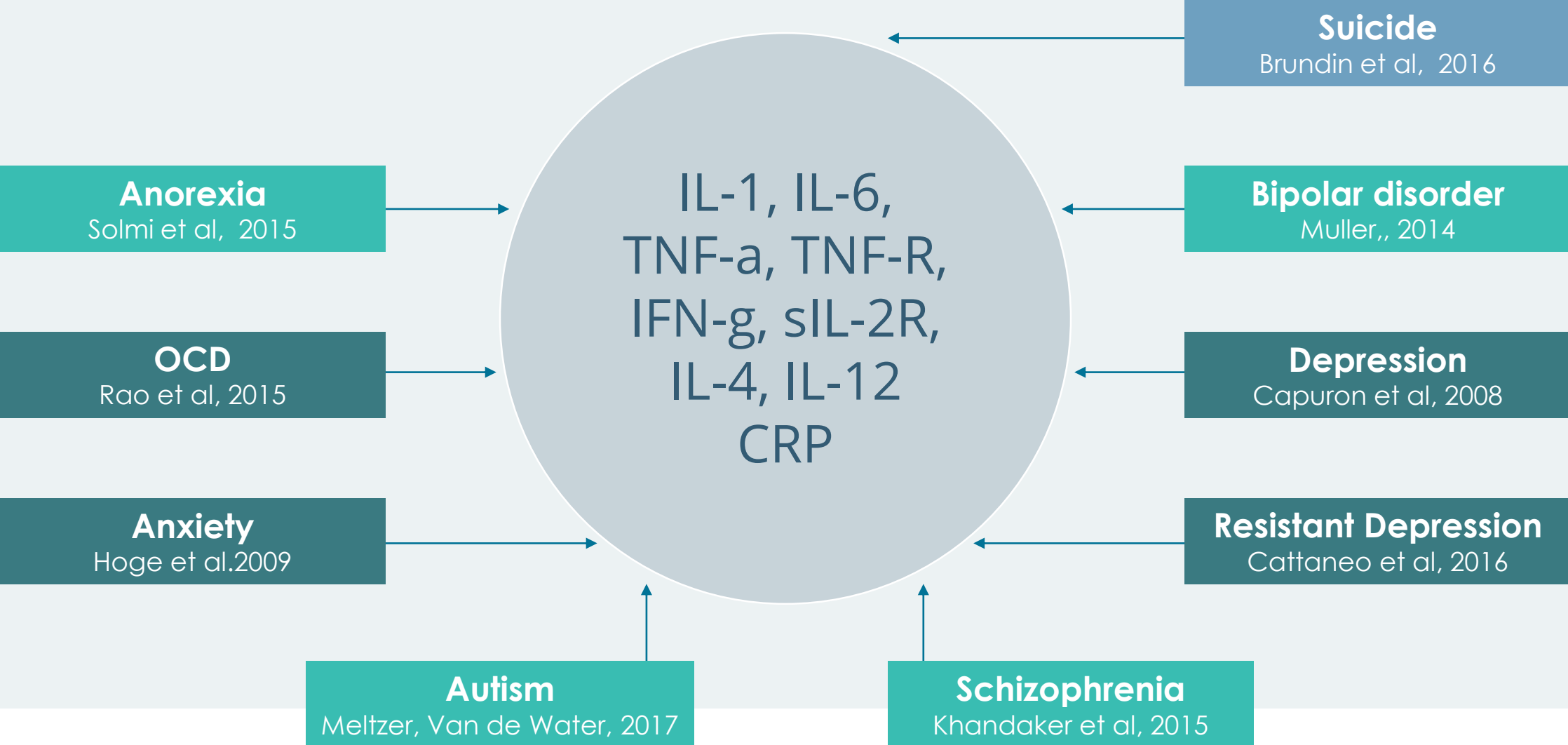
(1) a clear definition of patients who fall within the immunopsychiatric continuum;

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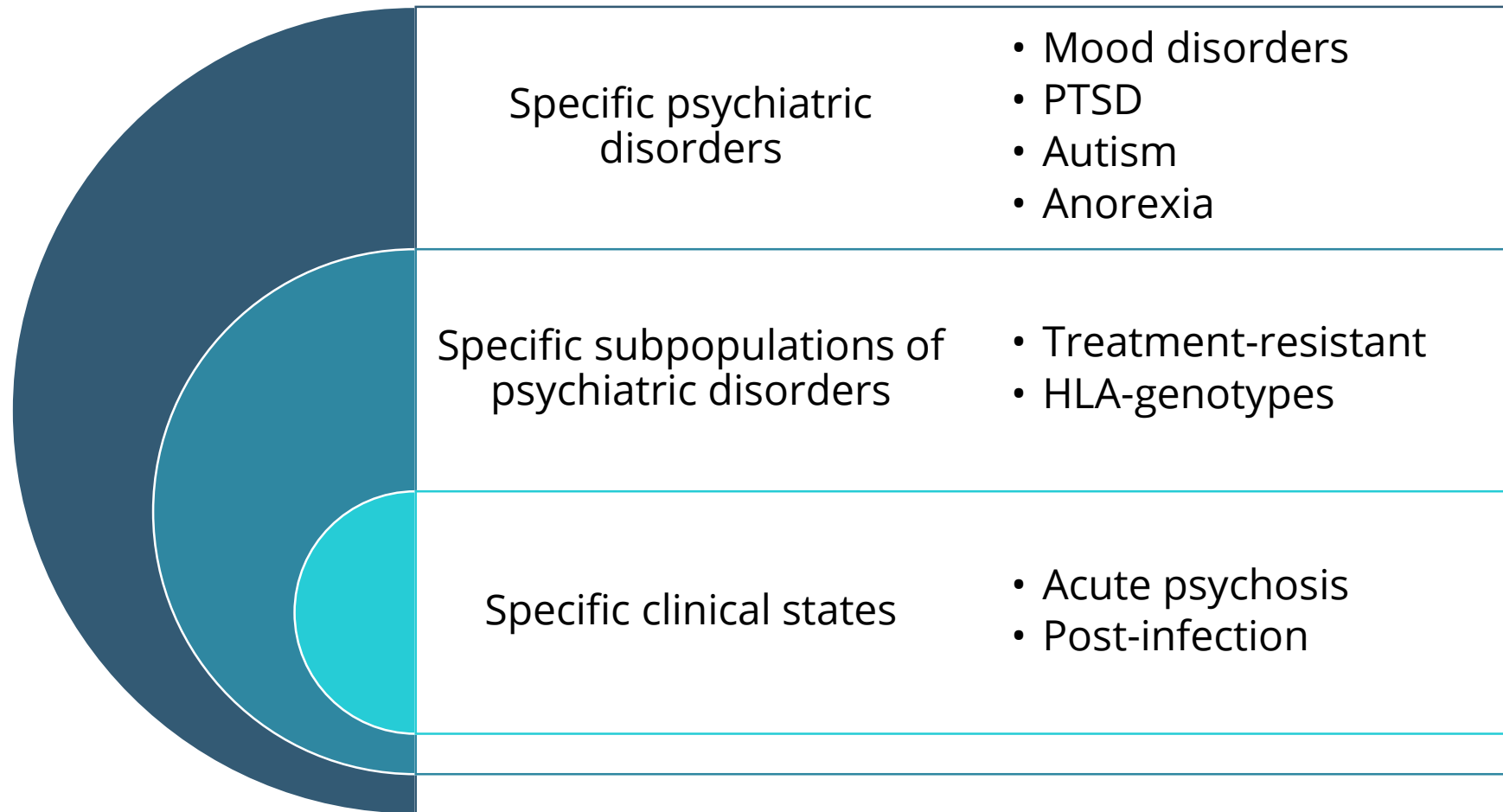
(3) convergence with other paradigms in biological psychiatry.



CYTOKINES CAN'T READ DSM OR ICD...



FOR WHICH PSYCHIATRIC PATIENTS ARE IMMUNE MECHANISMS RELEVANT?

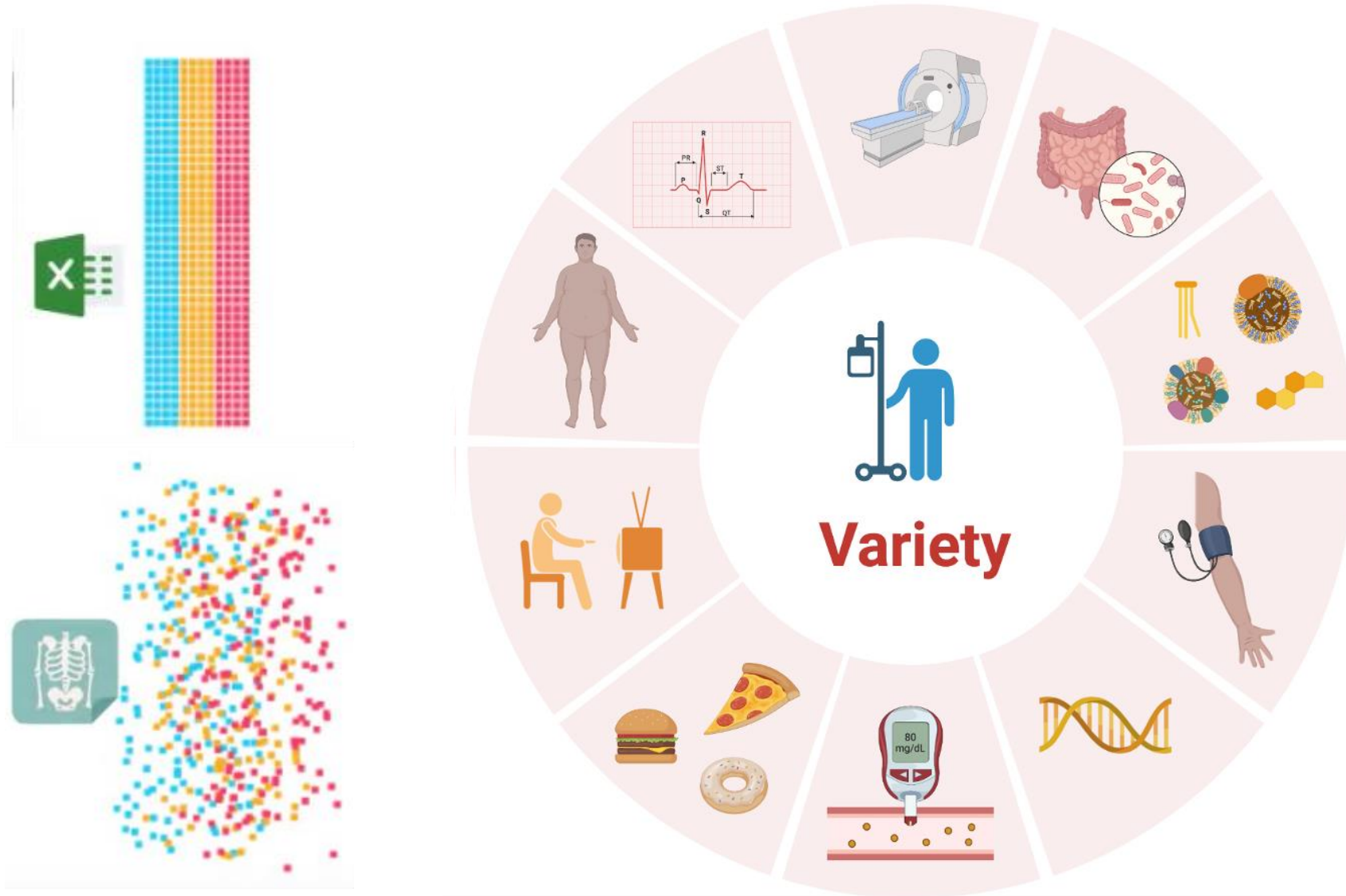


STATE-SPECIFIC IMMUNE CHANGES

Psychosis spectrum disorder patients demonstrate specific immunological changes during acute symptomatic states and in older age, not observed in younger and stable or remitted patients:

- Increased conc of IL6, IL8, IL1RA, TNF α , and CCL2 (De Picker et al. Front Immunol 2020)
- Increased ^{18}F -PBR111 TSPO PET uptake. Correlation PANSS-pos scores with regional V_T $r=0.767$. (De Picker et al. BBI 2019)
- Increased Iba1-positive microglia in dorsal PFC (De Picker et al. BBI 2021)
- Downregulation of the kynurenine pathway (Morrens et al. Schizophr Res 2020, Skorobogatov et al. BBI H, 2023)

Big Data in Psychiatry





Mega-analysis

Pooled databases: n= 12 RCT



ADVANTAGES

- Exploratory
- Heterogeneous data types
- Sample uncertainty <<<
- Interactive effects
- Non-linear effects



GOALS

- Prediction model of immune-mediated depression
- Clinical decision support tool
- Optimising future RCT designs

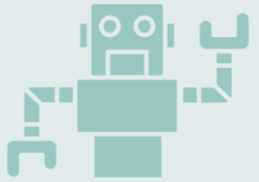
Machine Learning in Psychiatry

ML = algorithms that allow computers to learn from data to make predictions or decisions

Clinical implications:

- Earlier diagnosis
- Personalized treatment
- Risk factor identification

Requires big data sets



I-GIVE dataset (INSERM, Paris)

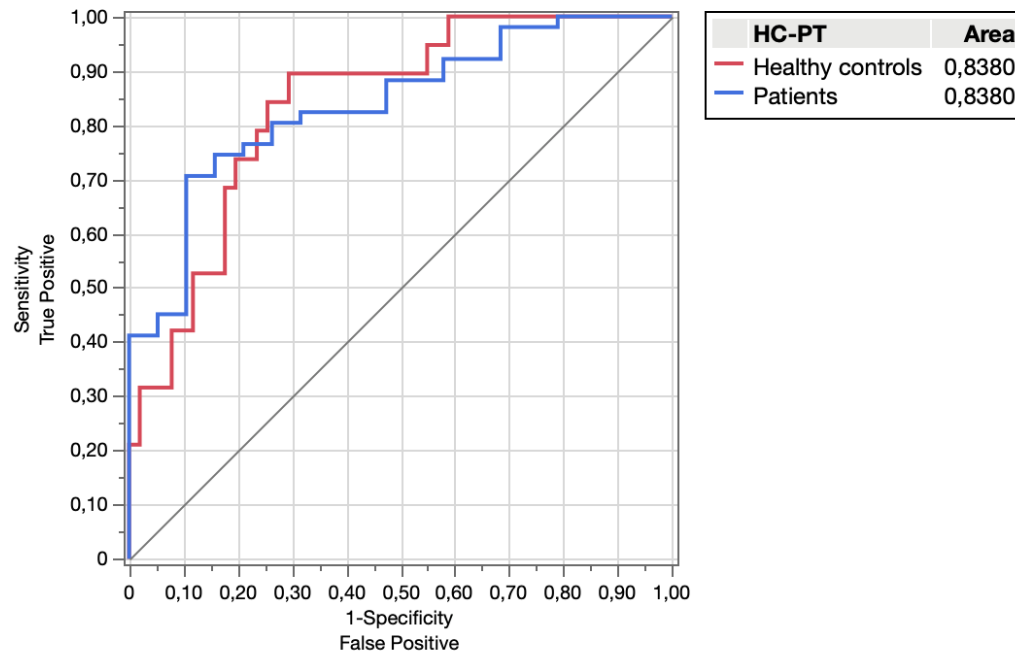
N = 186 schizophrenia (SCZ)

N = 321 bipolar disorder (BD)

N = 185 healthy control (HC)

Biomarkers for prediction of diagnosis and illness state

ROC-curve on Test Data

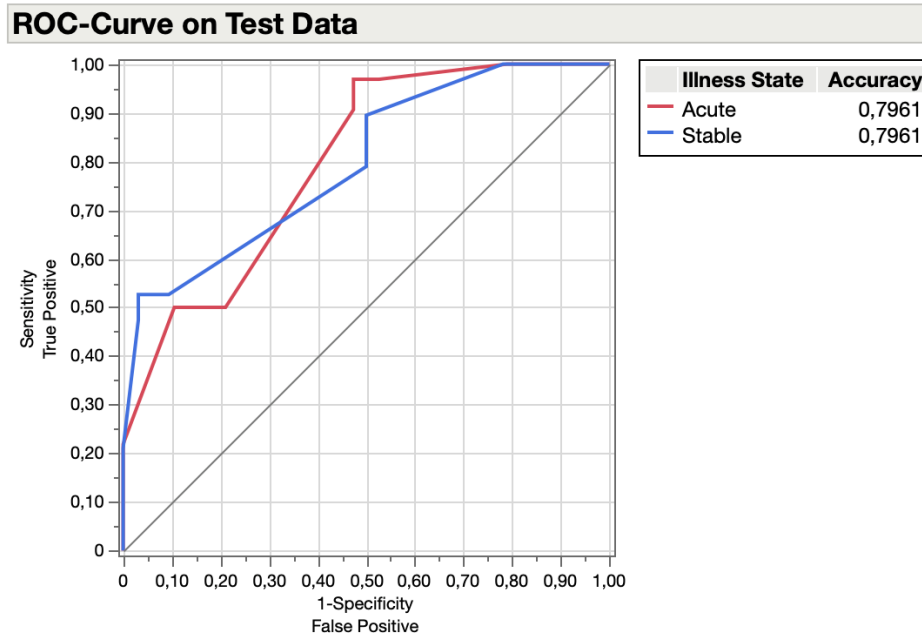
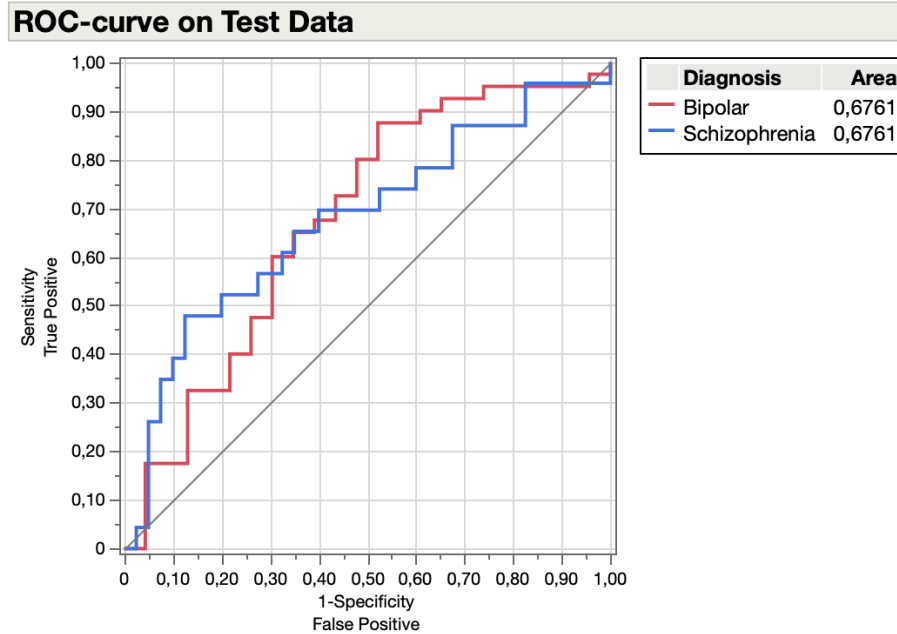


Panel of kynurenine metabolites and cytokines

HC vs. Patients (SCZ + BD)

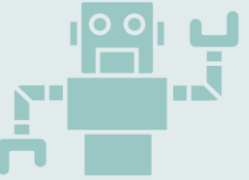
Accuracy of 83,8%

Biomarkers for prediction of diagnosis and illness state



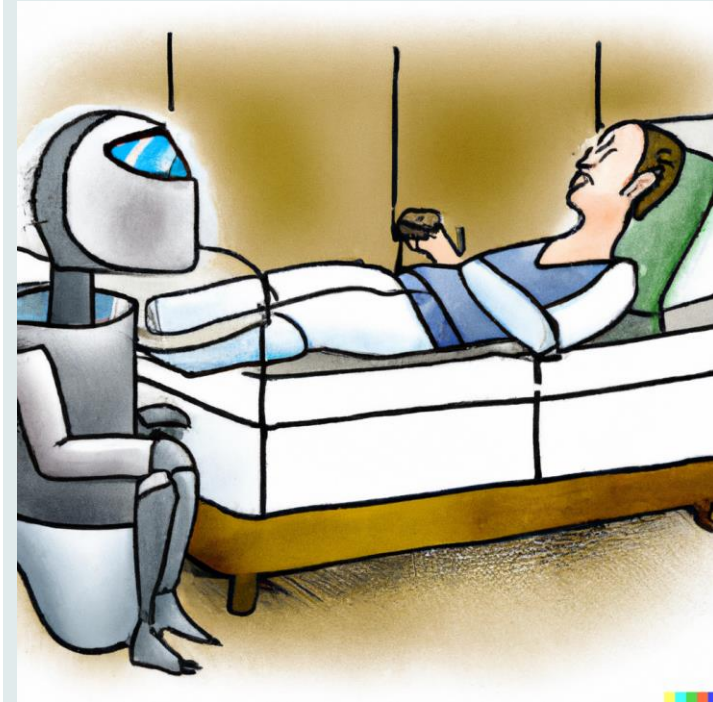
Panel of kynurenine metabolites and cytokines

- SCZ vs BD: 67,6%
- Acute vs Stable: 79,6%



Machine Learning in Psychiatry: Threats and Challenges

- Ethical considerations
 - Patient privacy
 - Safety
- Limitations in databases
 - Heterogeneity
 - Not always representative
- Interpretability of the results



Biomarkers for prediction of treatment response



Pharmacological treatment:

- MDD: poor response was predicted by higher baseline IL-6
- Lower kynurenine predicted response to Escitalopram

Electroconvulsive therapy:

- TNF-a, CRP and IL-6 predicted response in MDD/BD groups.
- Meta-analysis: no predictive cytokines, but a potential effect of kynurenine



Transcranial Magnetic Stimulation:

- Predictive capacity of oxidative stress markers

n = 80 patients, with (non) psychotic (bipolar) depression
Measured before and after an ECT treatment course:



Clinical questionnaires



Cognitive tests



Inflammatory Biomarker analysis

- Genome sequencing
- Transcriptomics
- Proteomics
- Cytokines
- Tryptophan metabolites
- Oxidative stress markers
- Growth Factors
- White blood cells



Biomarkers for prediction of treatment response

Electroconvulsive therapy (ECT)

&

Extensive inflammatory biomarker profile

3 critical milestones

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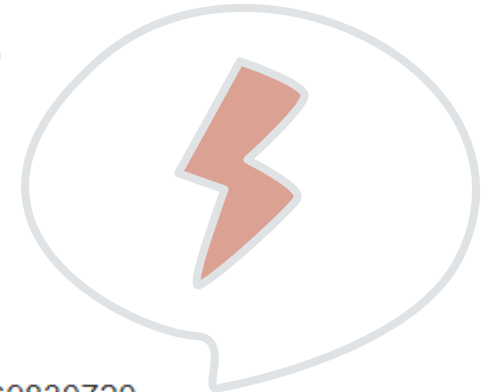


Biomarkers for treatment stratification in MDD



Immune-mediated MDD

- 1/3 of patients (hsCRP \geq 3 mg/L, (95% CI 21–34%) (Osimo et al 2019)
- Higher risk of treatment **non-response**
- More **somatic symptoms**: fatigue, changes in appetite, sleep...
- **Treatment?**



[Neuropsychiatr Dis Treat](#). 2023; 19: 1–25.

Published online 2023 Jan 5. doi: [10.2147/NDT.S385117](https://doi.org/10.2147/NDT.S385117)

PMCID: PMC9830720

PMID: [36636142](https://pubmed.ncbi.nlm.nih.gov/36636142/)

Anti-Inflammatory Treatment Efficacy in Major Depressive Disorder: A Systematic Review of Meta-Analyses

[Maria S Simon](#), ^{1, 2} [Gara Arteaga-Henríquez](#), ^{3, 4} [Ahmed Fouad Algendy](#), ^{1, 5} [Timo Siepmann](#), ^{1, 6} and [Ben M W Illigens](#) ¹

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INSTA-MD: INflammation-based Stratification for immune-Targeted Augmentation in Major Depressive disorder



2 x /day

Celecoxib 200 mg
Minocycline 100 mg
Placebo

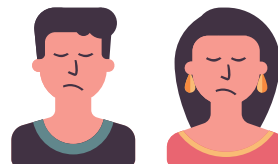


2 strata (hsCRP)
Immuno-subtype
of MDD



Augmentation
Treatment

- N = 240 patients
- MDD diagnosis
 - 14 \geq HDRS-17
 - Antidepressant treatment
- 18-65 years old



Stratified RCT designs: INSTA-MD

Multicenter Randomised
Controlled Clinical trial

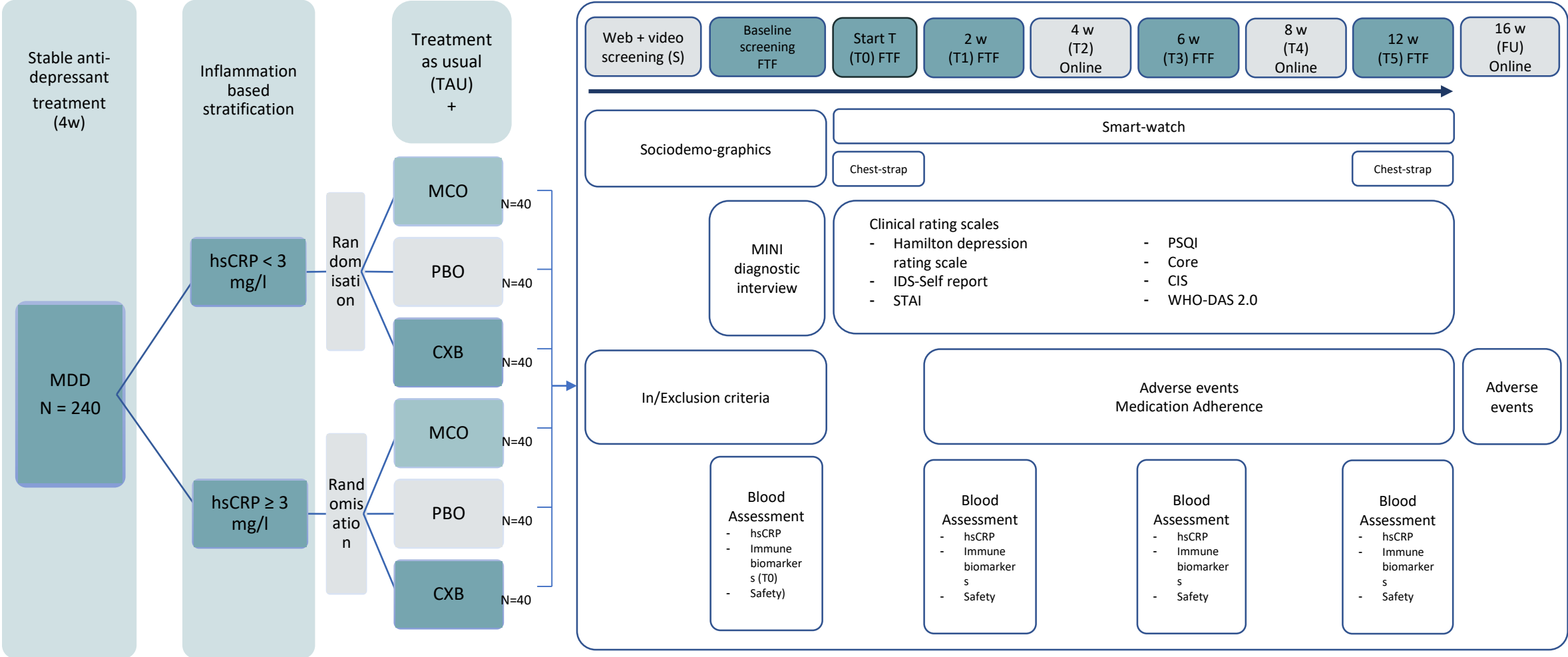
UPC Duffel
UZ Brussel
UPC KU Leuven

Inflammation based stratification
(hs-CRP)

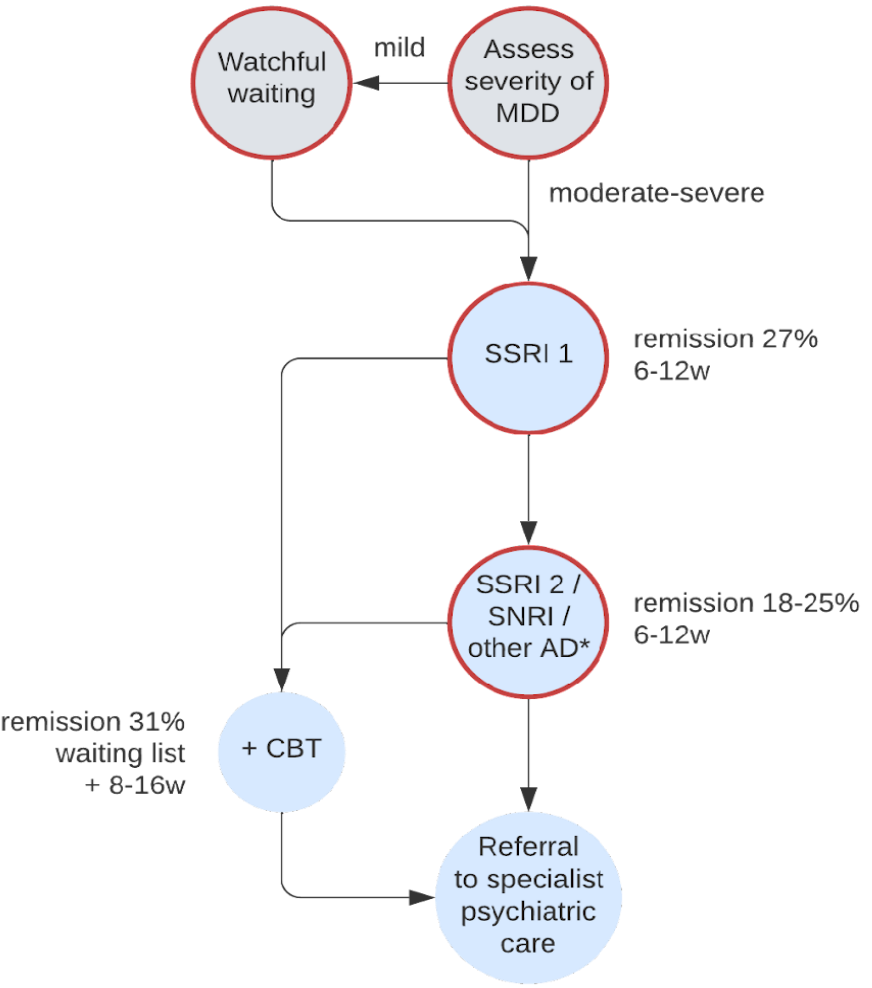
FWO TBM Project

Stratified RCT designs: INSTA-MD

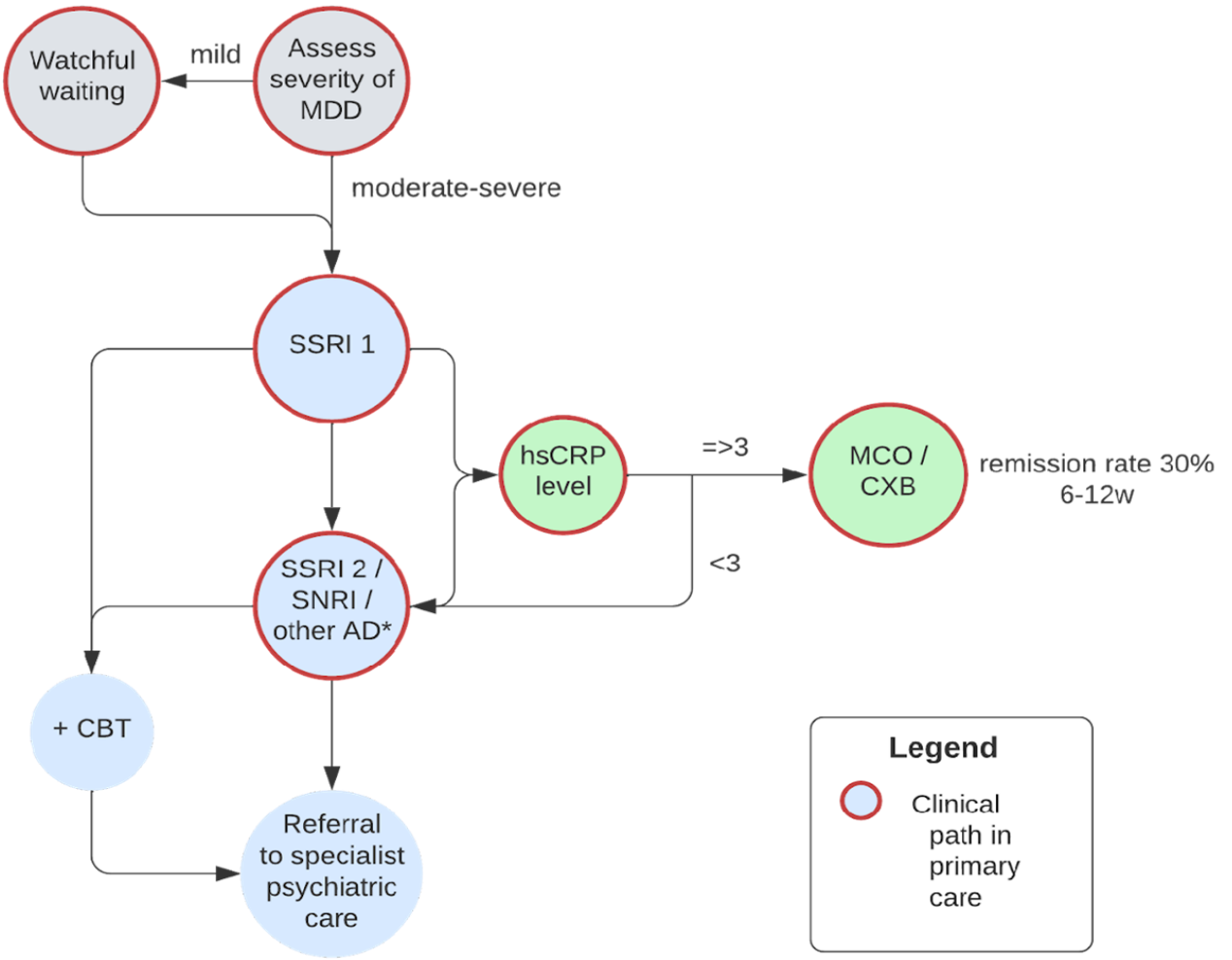
INSTA-MD: A RANDOMISED CONTROLLED CLINICAL TRIAL




[A] MDD clinical pathway TAU



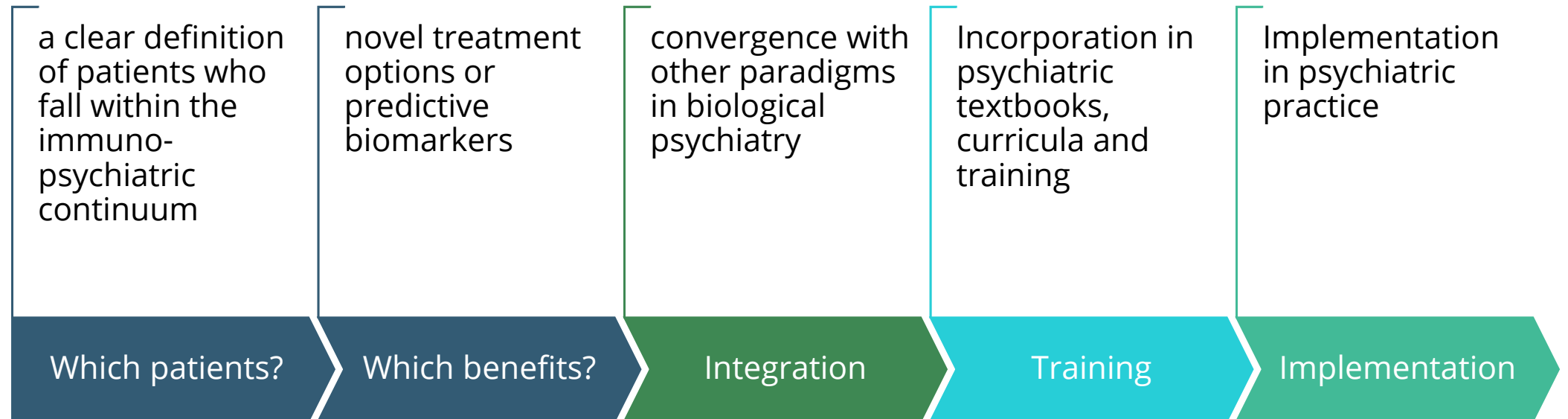
[B] MDD clinical pathway with immunotargeting in primary care



Legend

-  Clinical path in primary care

STRATEGIC TRAJECTORY

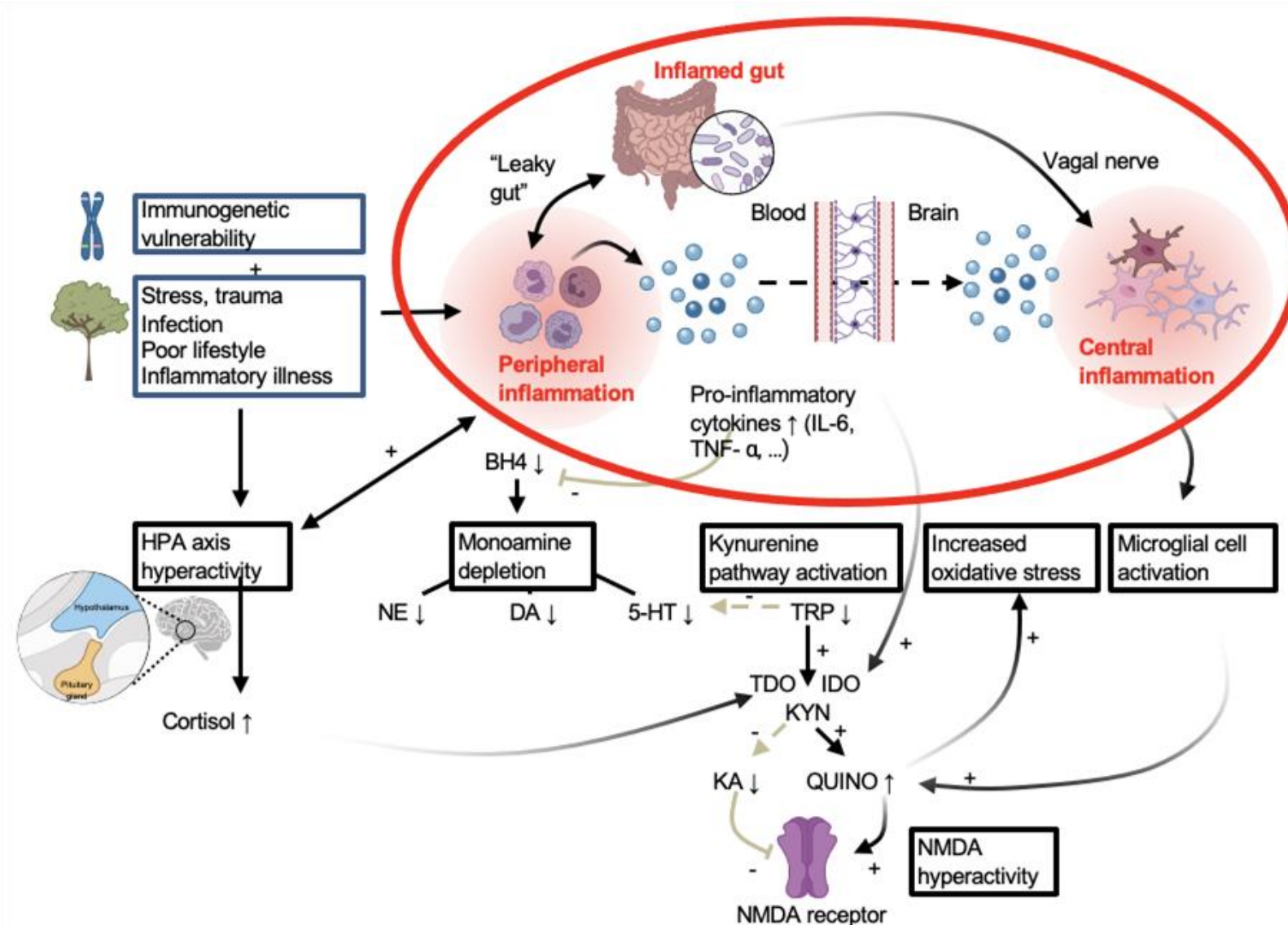


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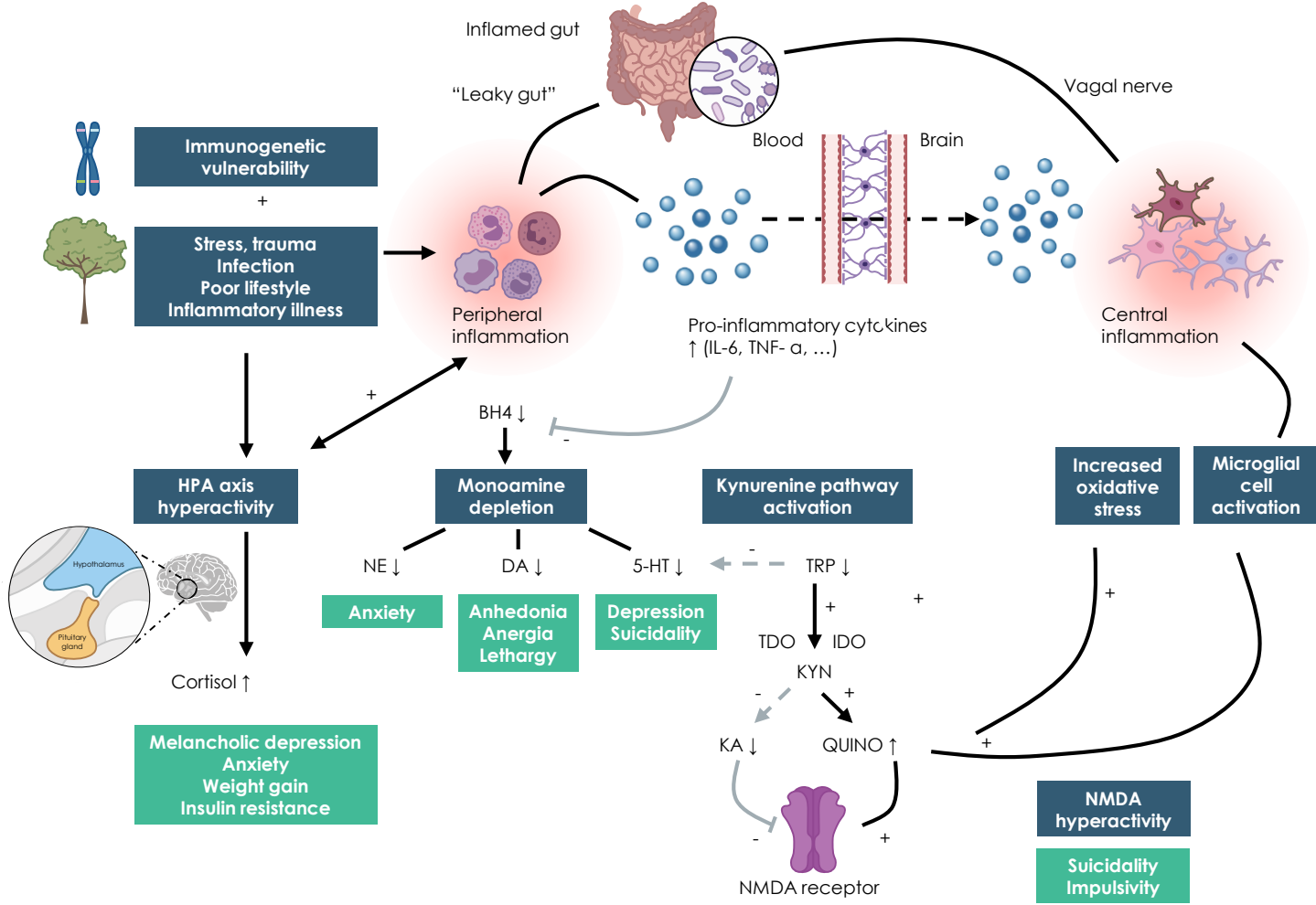


From inflammation to neurotransmitters abnormalities in MDD



5-HT, serotonin;
 BH4, tetrahydrobiopterin;
 DA, dopamine;
 HPA, hypothalamic-pituitary-adrenal;
 IDO, indoleamine-2,3-dioxygenase;
 IL, interleukin;
 KA, kynurenic acid;
 KYN, kynurenine;
 MDD, major depressive disorder;
 NE, norepinephrine;
 NMDA, N-methyl-D-aspartate;
 QUINO, quinolinic acid;
 TDO, tryptophan dioxygenase;
 TNF, tumour necrosis factor;
 TRP, tryptophan.

Inflammation in depression



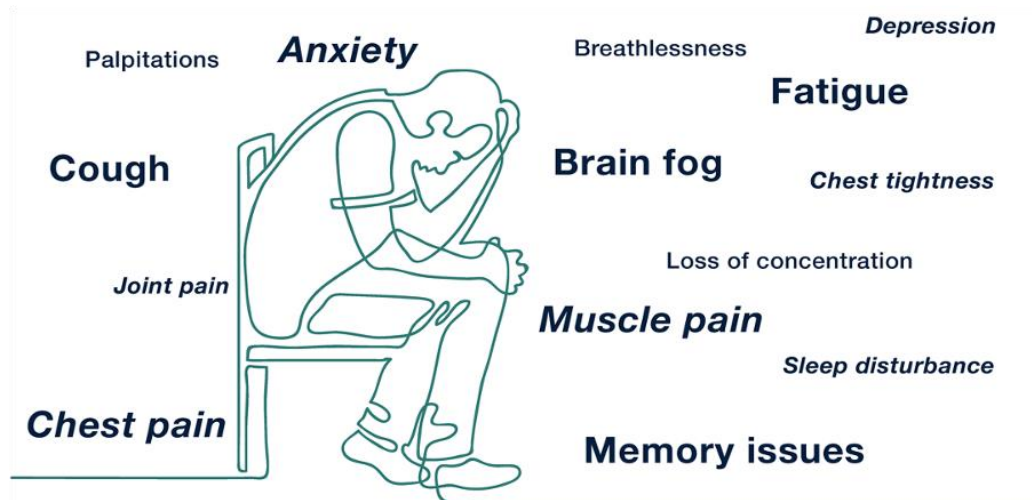
The link between biological disturbances and transnosographical dimensions...

COVID-19 AS CATALYST FOR PROGRESS



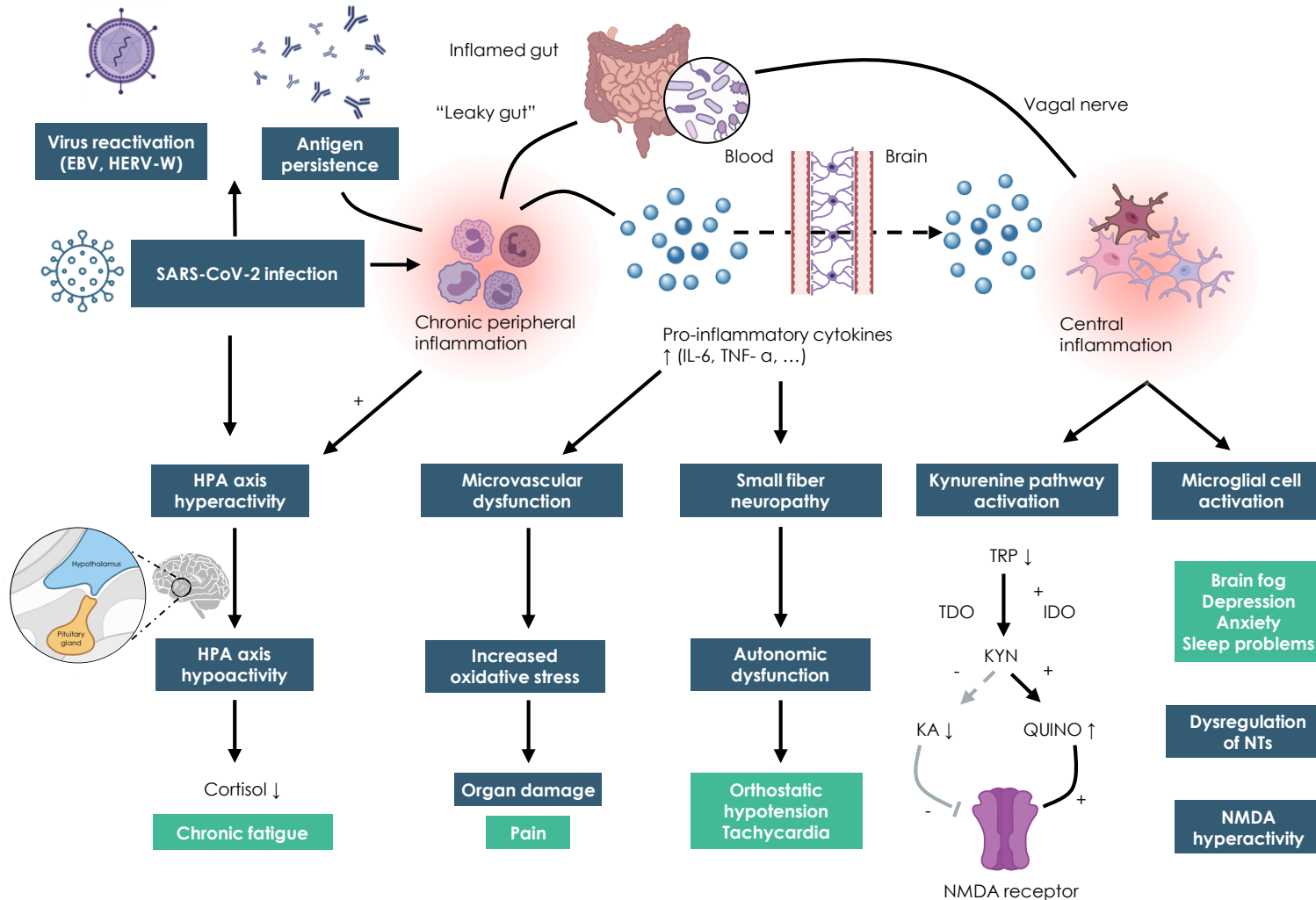
Long COVID syndrome

- WHO: “post COVID-19 condition”
 - Persistent symptoms 3 months from the infection, lasting at least 2 months
 - Not explained by an alternative diagnosis
- Multi-organ disorder, heterogenous
- After 6 months: 1/7
- In asymptomatic, mild and severe cases, but more likely when hospitalized



Adapted from: <https://www.psychiatrycentre.co.uk/treatments/long-covid/>

COVID-19 and mental illness

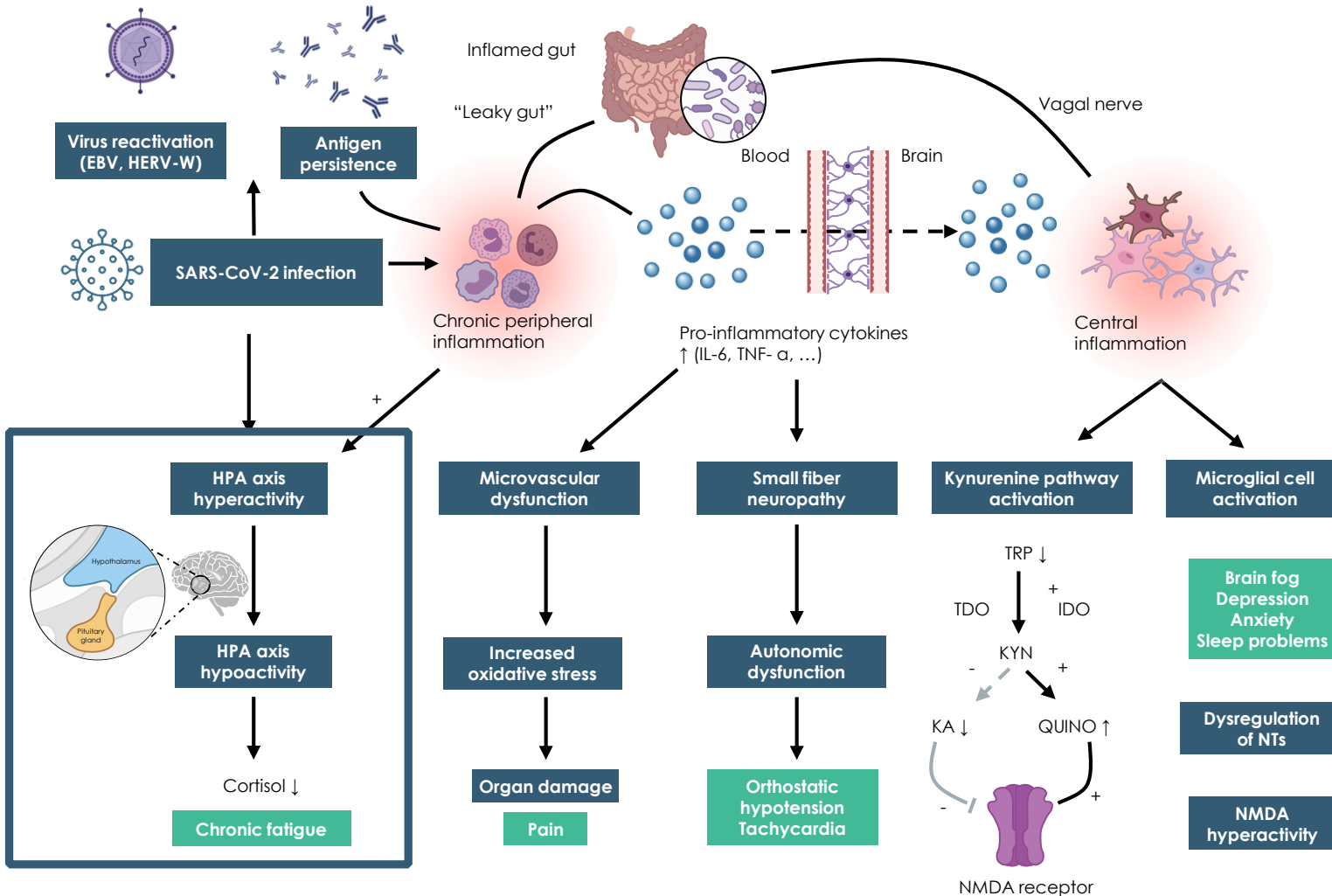


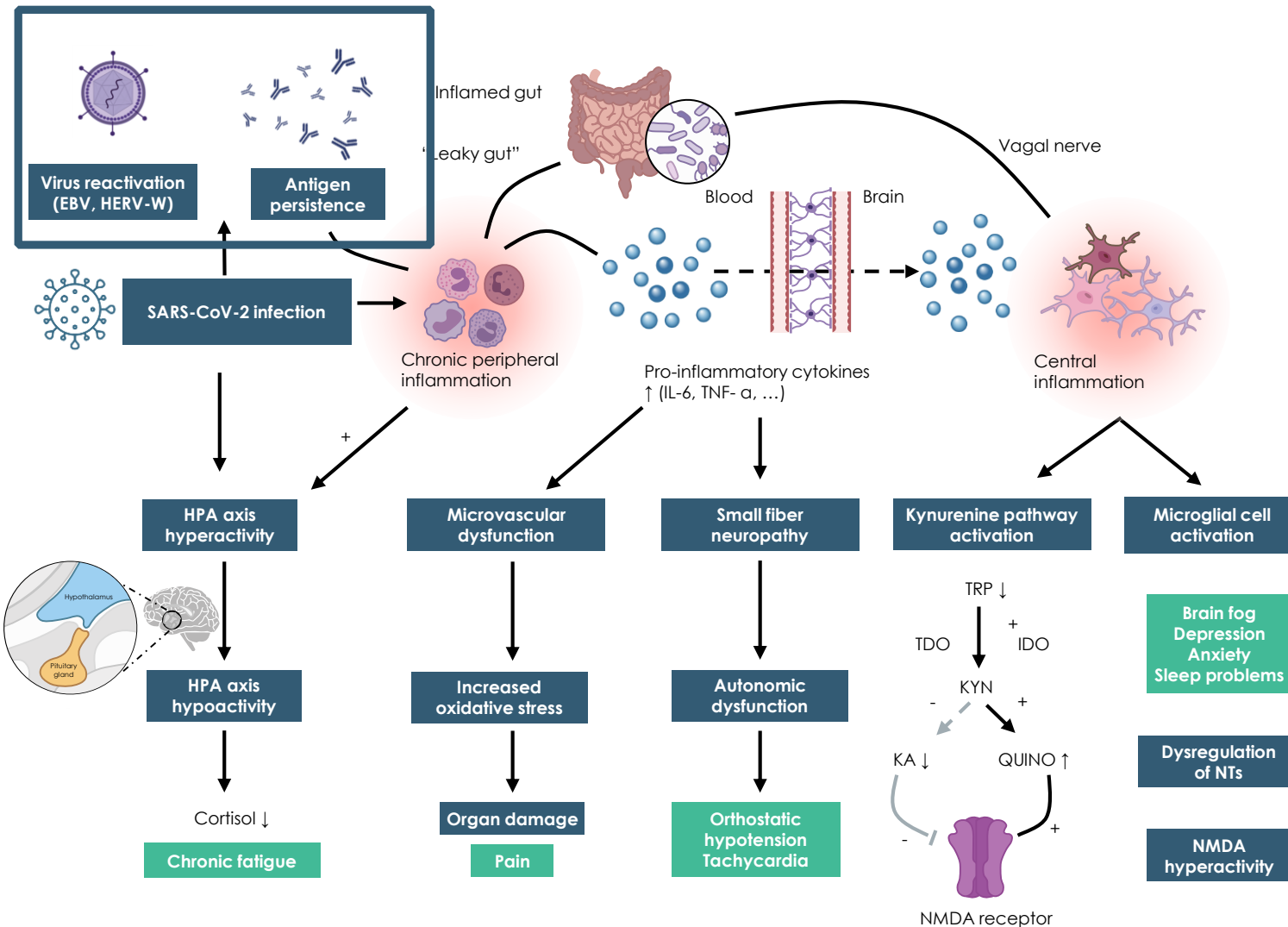
- 3 months after COVID-19 (Premraj et al., 2022)
 - 37% fatigue
 - 31% sleep disturbances
 - 32% brain fog

- Persistent elevated levels of IL-1 β , IL-6, TNF- α in long COVID (Schultheiss et al., 2022)

HPA-axis hypoactivity

- Plasma cortisol levels 50% lower in long COVID vs. controls (Klein et al, preprint)
- Also hypocortisolism shown in
 - Chronic fatigue syndrome (Van Den Eede et al, 2007)
 - Fibromyalgia (Lin et al, 2021)
 - Stress-induced exhaustion syndrome (SED) (Wahlberg et al, 2009)





Virus reservoirs

- Persistence of SARS-CoV-2 antigen

Virus reactivation

- HERV = Human Endogenous RetroVirus
 - 8% of human DNA
 - HERV-W-ENV = Envelope protein
 - Neurotoxic effects
 - HERV-W-ENV activated in MS, schizophrenia and bipolar disorder (Morandi et al, 2017; Tamouza et al, 2021)

- EBV reactivation (Gold et al, 2021)

n = 50 long COVID
n = 50 COVID controls
n = 30 non-COVID controls

observational, longitudinal study



**Clinical
questionnaires**



**Cognitive
battery test**



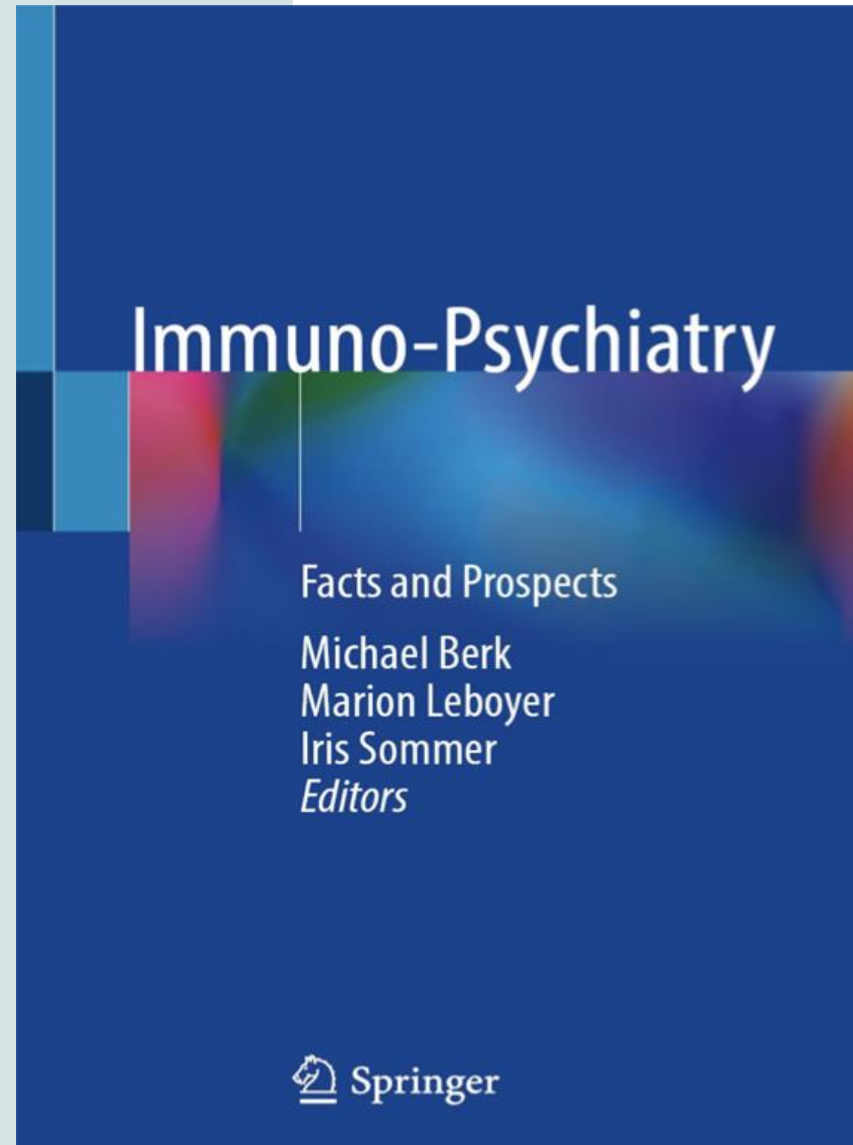
**Biomarker
analysis**

Cortisol (CAR)
SARS-CoV-2 AB
HERV-W-ENV
Kynurenine pathway
White blood cells
Cytokines

Cov-N-Psy

**Neurobiological
underpinnings of
neuropsychological
symptoms in long
COVID**

To find out more...



THE FUTURE OF IMMUNOPSYCHIATRY



Immuno-NeuroPsychiatry
ECNP Network

Immunopsychiatrie!

Ga naar: <https://www.menti.com/albdo1zidunx>

Of scan:



MANY THANKS TO



THE FUTURE OF IMMUNOPSYCHIATRY

SINAPS UPCD

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- Alysia Van der Saet
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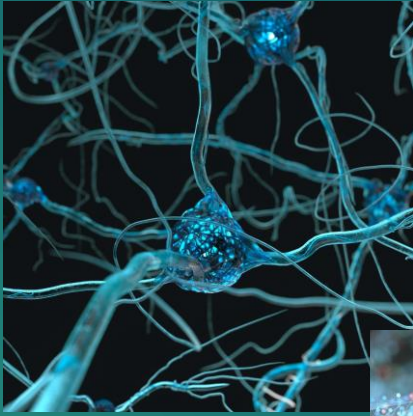
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- Alexandre Lucas
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- Jean-Romain Richard
- Marianne Foiselle

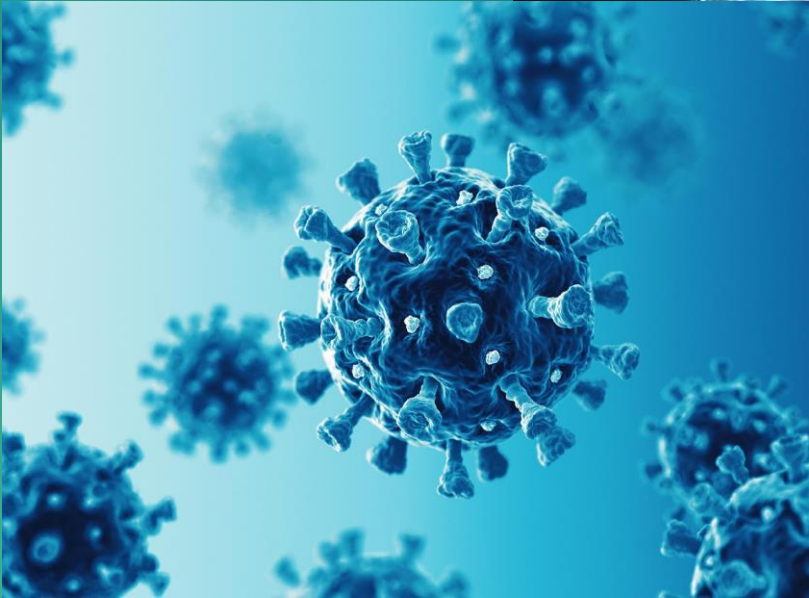


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THANK YOU

