Advanced Methods for Human Neuromodulation

Glutamatergic Regulation for Psychosis Reduction - A TI and MRS Study

Group 6

EPFL

Summary

1. Psychosis - Background
2. Hypothesis
3. Goal of the Study
4. Cohort
5. Study Design
6. Expected Results
7. Risks and Limitations
8. Conclusion and Outlook

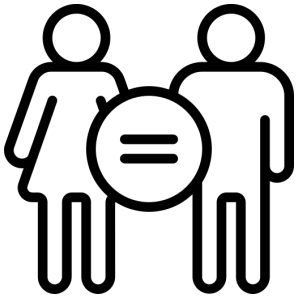
Psychosis Background

1:100

Prevalence of Psychosis

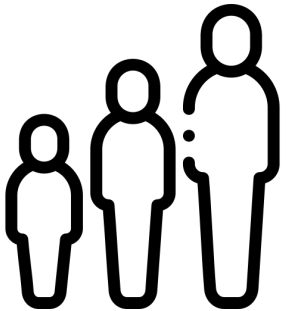
EQUAL

Gender Prevalence



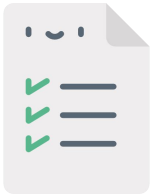
ONSET OF FIRST EPISODE PSYCHOSIS

18 - 25 years old



Psychosis - Symptomatology

Amalgamation of psychological symptoms resulting in a **loss of contact with reality**.



At least **2 / 5** DSM-V criteria

Positive Symptoms

- Delusions
  - Beliefs of being followed, monitored, having abilities…
- Hallucinations
  - Visual, auditory or somatosensory
- Disorganized thoughts & speech
- Disorganized behaviour

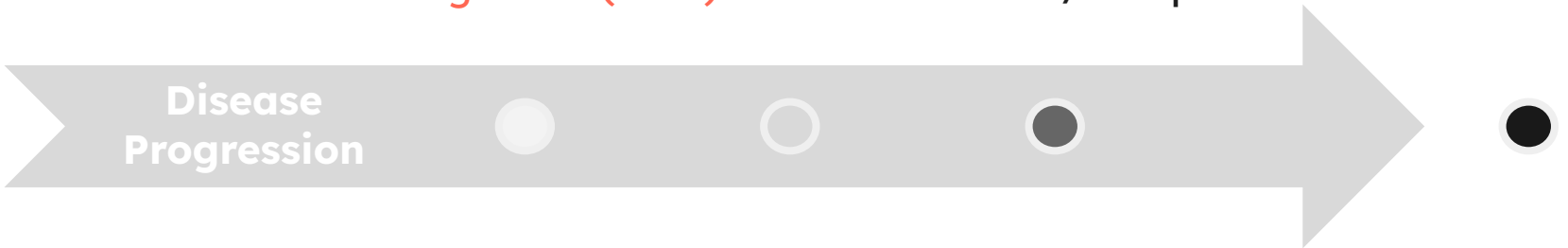
Negative Symptoms

- Loss of normal functioning:
  - Apathy
  - Impaired speech
  - Reduced motivation & initiation

Psychosis Spectrum

Stage 1 - Prodromal Phase
Ultra High Risk (UHR)

Stage 3 - Recovery
Remission/Relapse



Stage 2 - Acute Phase
First Episode of
Psychosis (FEP)

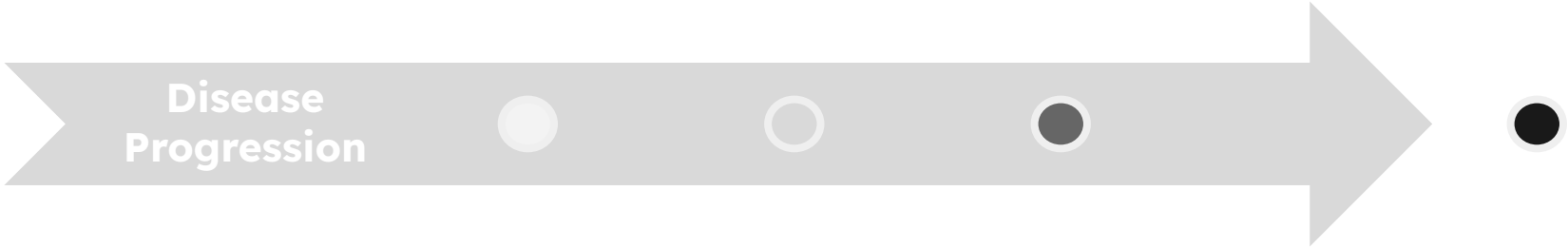
Stage 4 - Persistent
Psychotic Disorder
(e.g. Schizophrenia)

30% conversion

Gee et al., 2014

Psychosis Correlates

Cognitive correlates of decline
Working Memory (WM),
Executive Function, Language



Neural correlates of decline
Atrophy, neurotransmitter imbalance

Sun Kim et al., 2011

Working Memory (WM) Deficits

Impairments

- Retaining information over short periods
- Using information to guide behavior/decision-making

Neural Correlates

- Dysfunction in **DLPFC**
- **Connectivity** issues
- **Neurotransmitter imbalances**

Clinical Implications

- Marker of progression
- **Predictive value**

Rossi et al., 2016

Brain Regions

Prefrontal Cortex

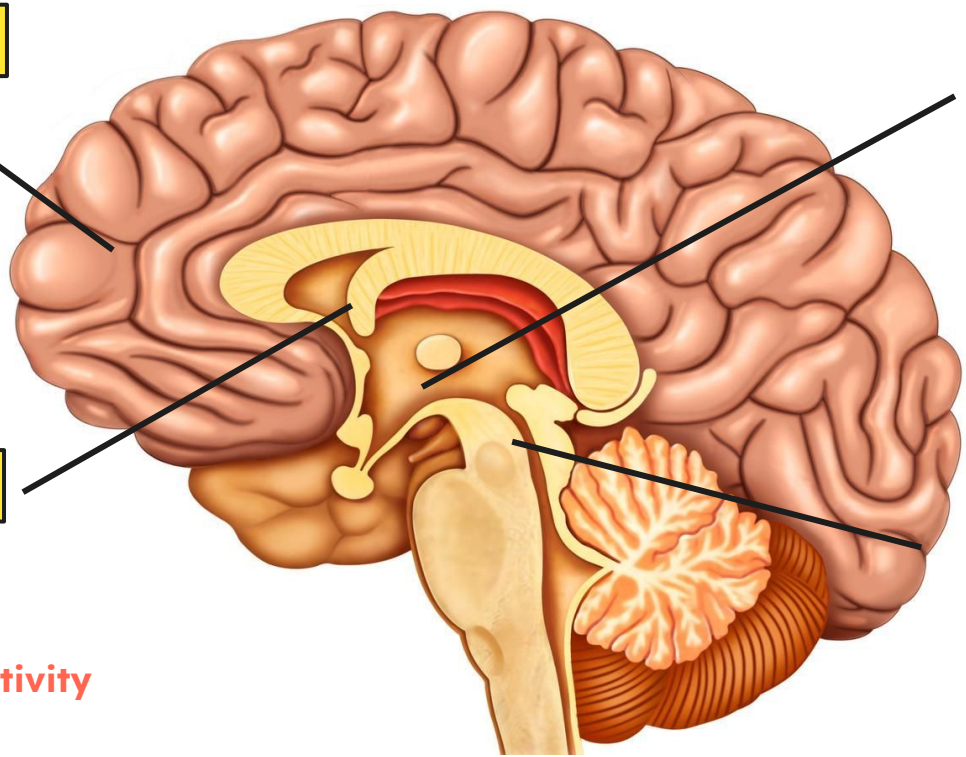
Decision-making
Working memory
Goal-directed behavior

Hypoactivity in DLPFC → cognitive deficits

Striatum

Reward processing
Habit formation

Hyperdopaminergic activity



Thalamus

Relay for sensory and cognitive information

Impaired thalamic filtering → sensory overload

Hippocampus

Memory formation
Context processing

Hyperactivity → generation of delusional thoughts

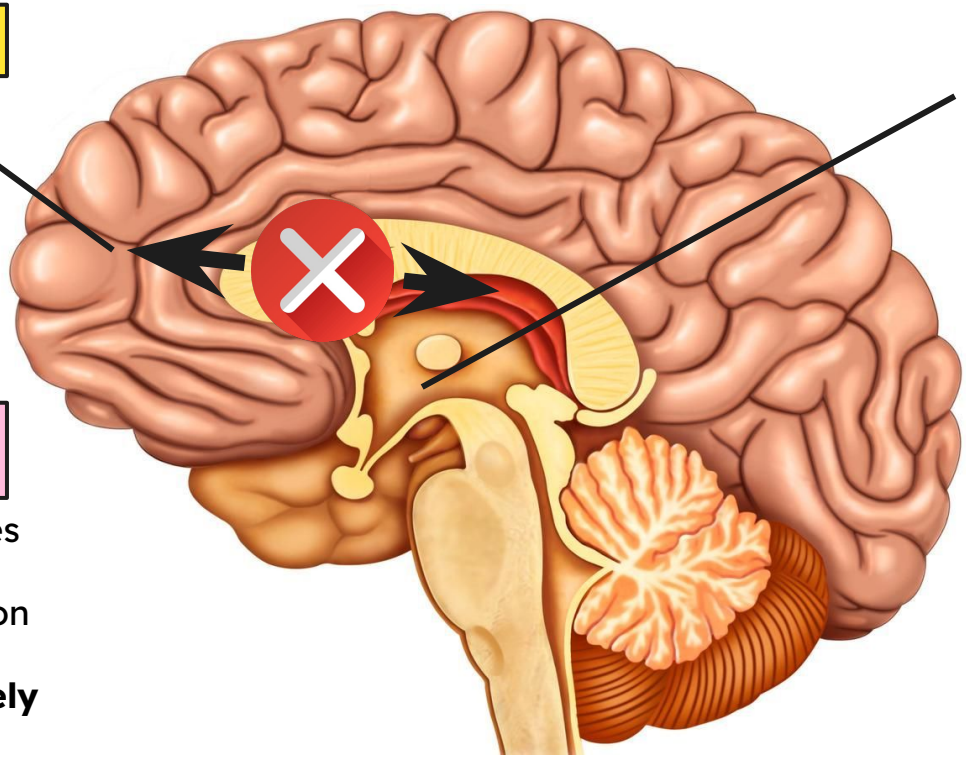
Brain Regions - WM Deficits

Prefrontal Cortex

Decision-making
Working memory
Goal-directed behavior

Thalamus

Relay for sensory and cognitive information



Dysfunctional Connectivity

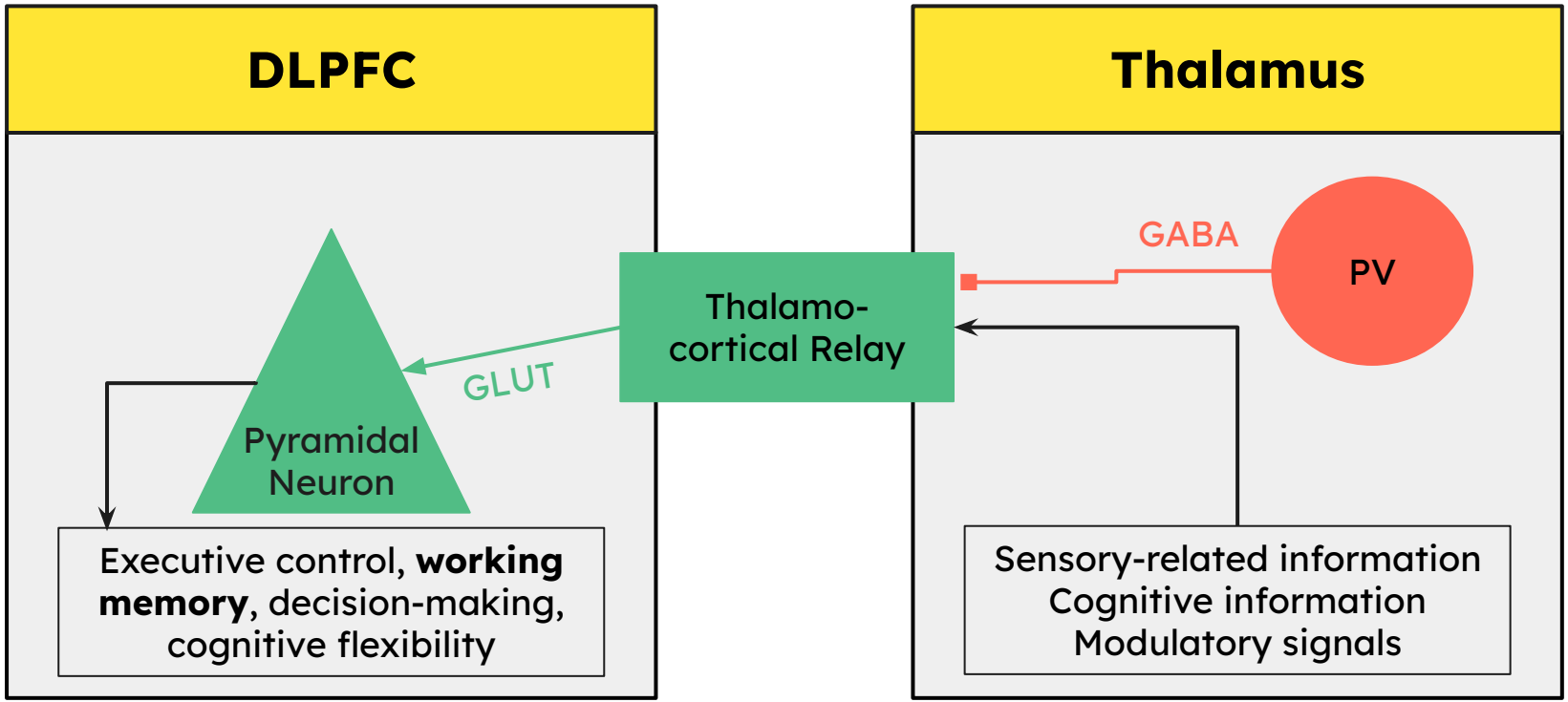
→ shown by fMRI studies

Disrupted communication

DLPFC cannot effectively maintain and update task-relevant information

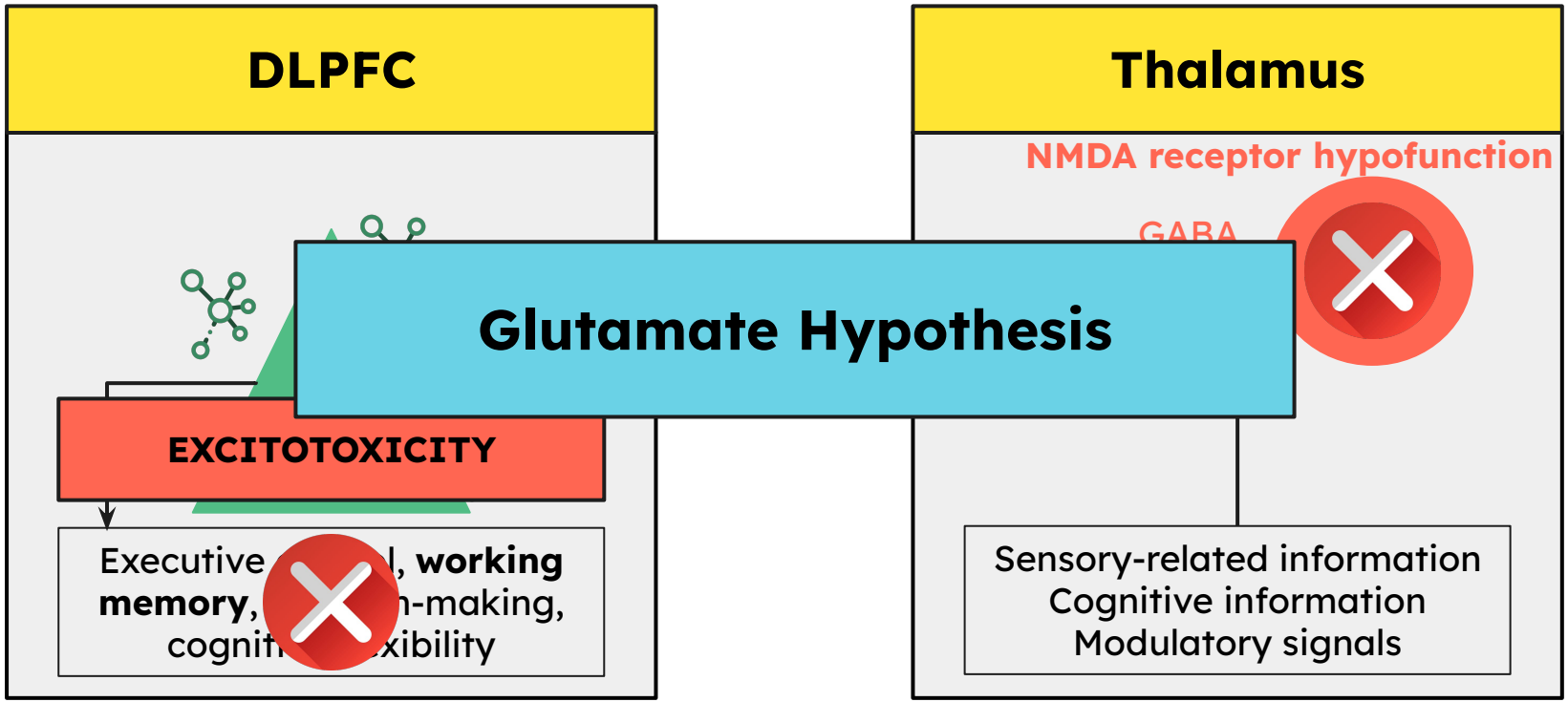
Woodward et al., 2012

Pathophysiology - Healthy



Plitman et al. 2014, Sharp et al. 2001, Tomitaka et al. 2000

Pathophysiology - Psychosis



Shah et al. 2020

Plitman et al. 2014, Sharp et al. 2001, Tomitaka et al. 2000

Psychosis - Treatments

Psychological Therapy
E.g., cognitive behavioral therapy

Antipsychotics
→ dopamine and serotonin as main targets

→ Positive symptoms

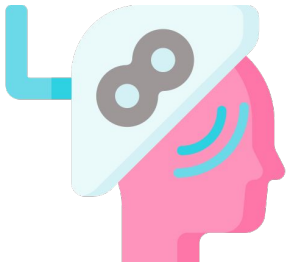
→ Only delays progression

+

Side effects !
worsened cognitive functioning
Ethical considerations !

Tandon et al. 2011
Liu et al. 2013
Allott et al. 2024

Psychosis - Treatments



TMS

tES

Mostly targeting **DLPFC**

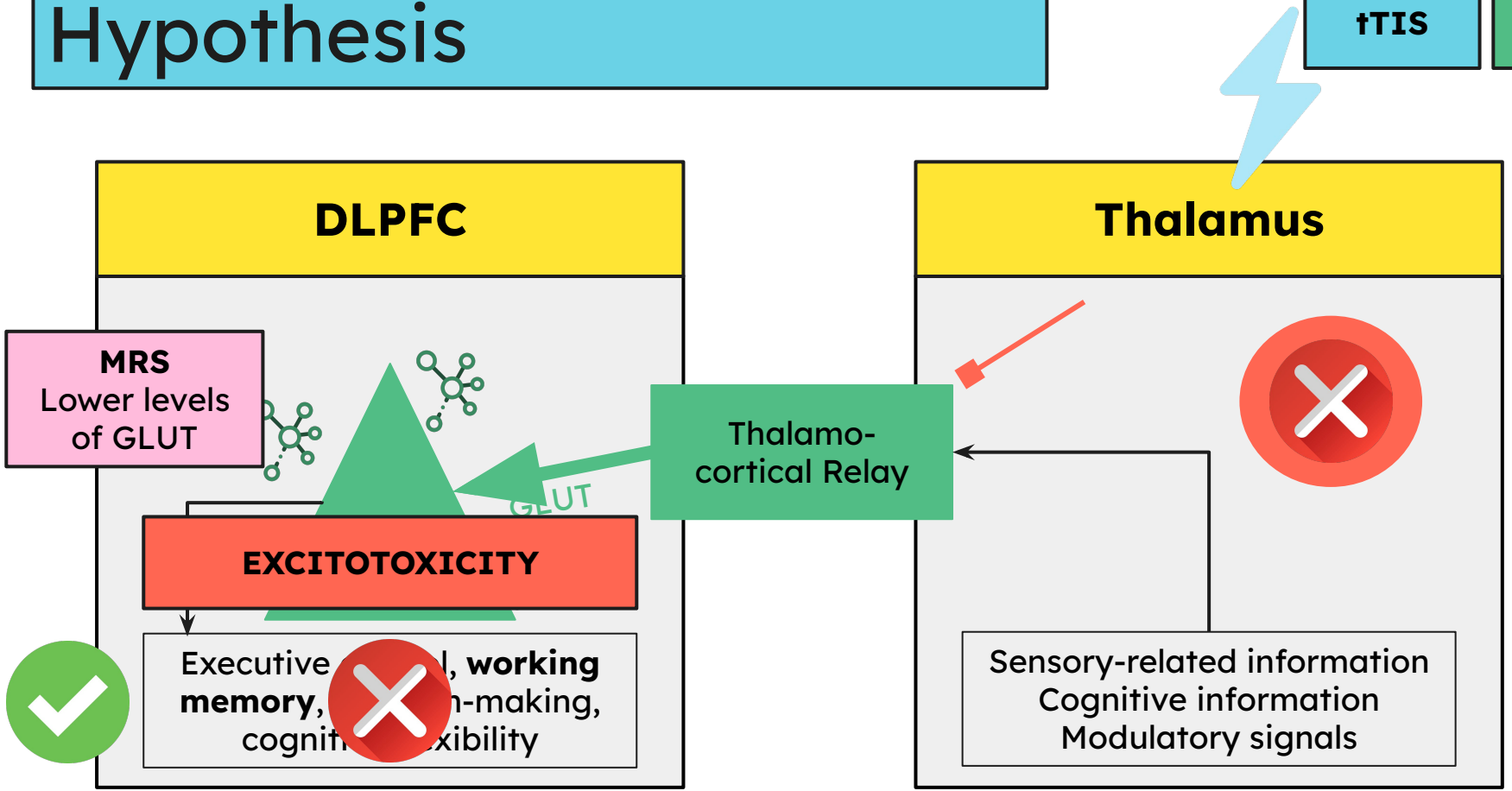
✓ Working memory performance improvements

? Heterogeneous results

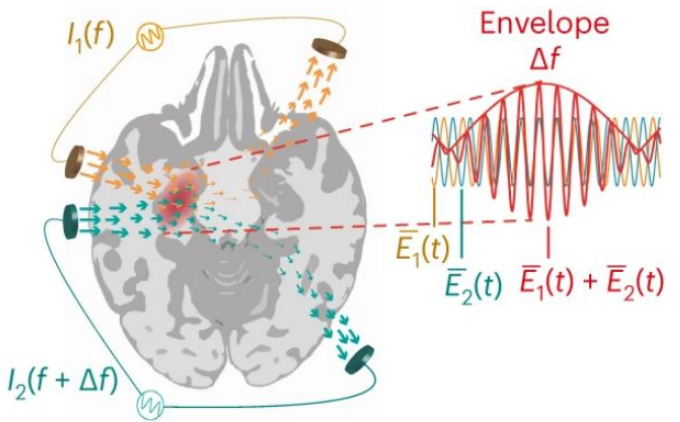
Liu et al. 2021
Manfredi et al. 2023

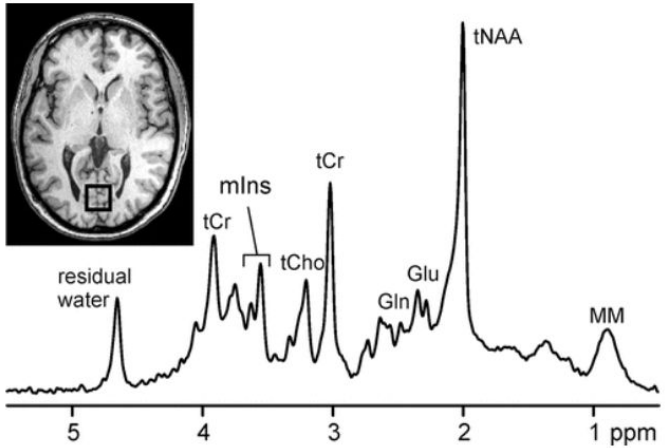
→ Other solutions ? Innovative techniques ? Other brain areas ?

Hypothesis


DLPFC
Thalamus
MRS
Lower levels of GLUT
Thalamo-cortical Relay
GLUT
EXCITOTOXICITY
Executive
, working memory,
n-making, cogniti
xibility
Sensory-related information
Cognitive information
Modulatory signals

Relevant Techniques





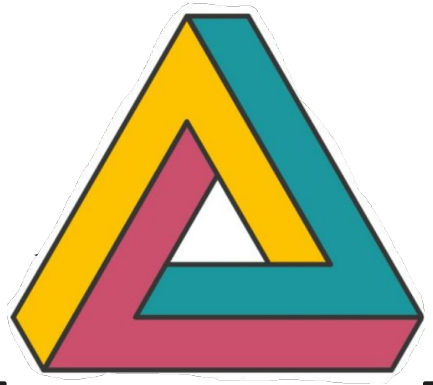
Transcranial Temporal Interference Stimulation (tTIS)

Magnetic Resonance Spectroscopy (MRS)

Goals Study

Three Distinct Goals

1. Measure glutamatergic levels in L-DLPFC



2. WM changes using TI and task targeting the Thalamus

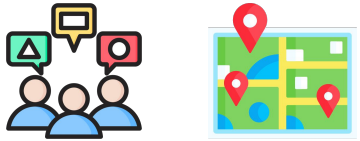
3. Impact on progression of disease

Cohort

Ultra High Risk (UHR)

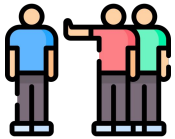
- Drug naive
- No compensatory pathways, no structural changes, no confound of chronicity
- Understand biological etiology

Heterogeneity



- N = 100
- Multicenter
- UHR patients only

Exclusion criteria

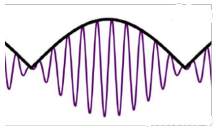


- Glutamatergic inhibitors
- DA inhibitors
- Epileptic history
- TBI
- Drug and substance use
- Paranoia

Keshavan et al. 1992, Prakash et al. 2023, Inchausti et al. 2023

Experimental groups

Active Group



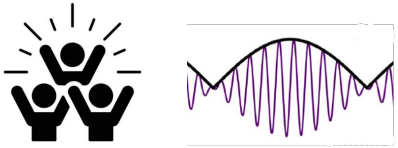
- Ultra High Risk patients
- **TI** stimulation of the **thalamus**

Ultra High Risk - Criteria

- CAARMS : Comprehensive Assessment of At Risk Mental States
- Recruit using CAARMS guidelines

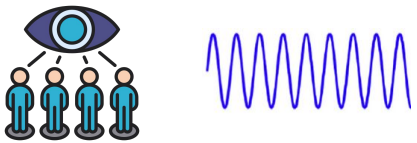
Experimental groups

Active Group



- Ultra High Risk patients
- **TI** stimulation of the **thalamus** (LTD)

Control Group



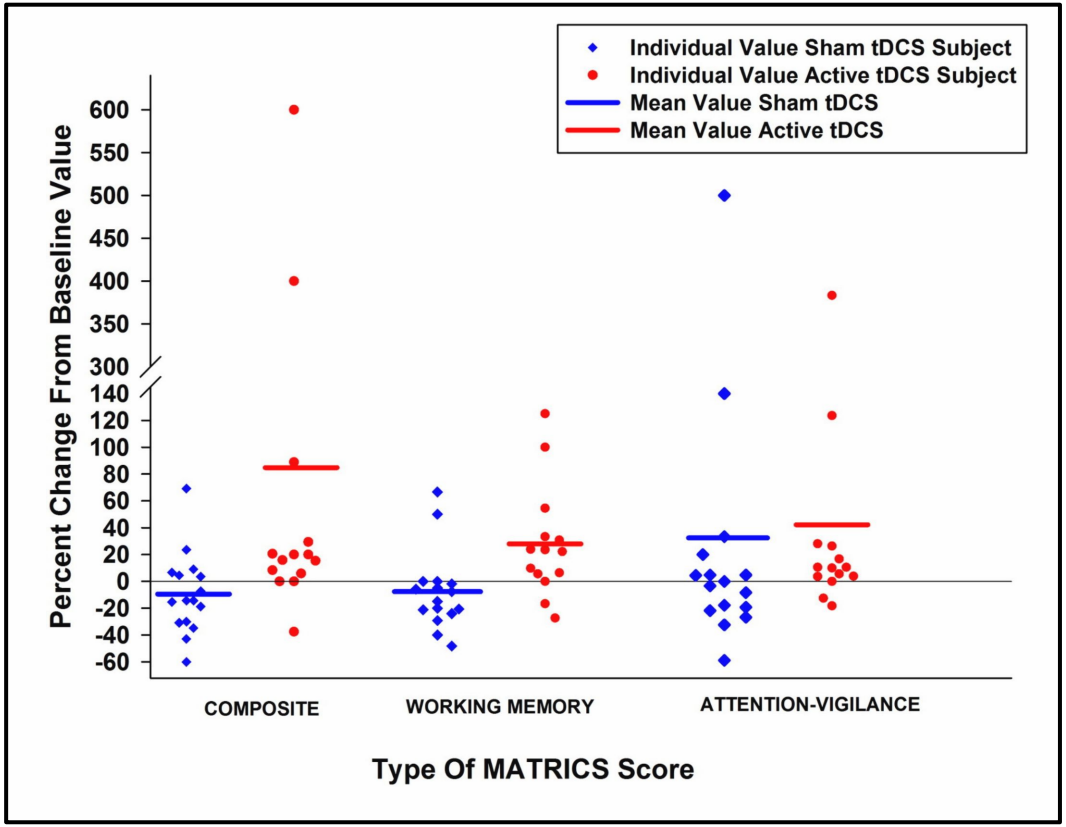
- Age and sex matched UHR
- **Sham** TI stimulation **(HF)** for optimal control of Placebo effect

Previous Stimulation Designs

Meta-analysis shows significant effects on WM targeting DLPFC using tDCS in schizophrenia:

- Safety in psychosis
- Duration of study
- Frequency of session

Chang et al., 2016 (2x/week, 16 weeks) **=>**



Timeline of Study

1. Main Study **2. Longitudinal Outcomes**

Baseline:
- MRS
- Untrained task
- sMRI
- CAARMS & PANSS

Treatment:
- TI
- Trained task

Post-test:
- MRS
- Untrained task
- sMRI

Post-Screening:
- MRS
- Untrained task
- CAARMS & PANSS

1. Decrease in Glutamate?

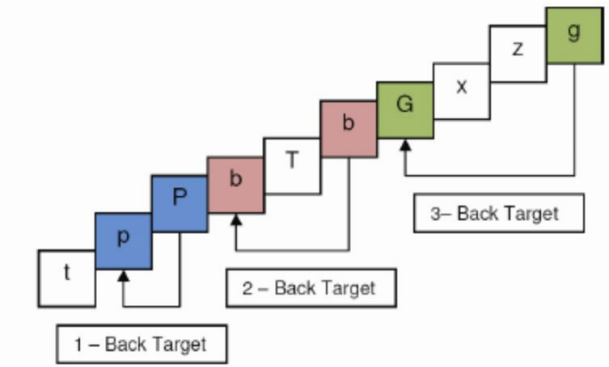
2. Improve working memory?

3. Decrease conversion rate to psychotic disorder?

N-Back Task

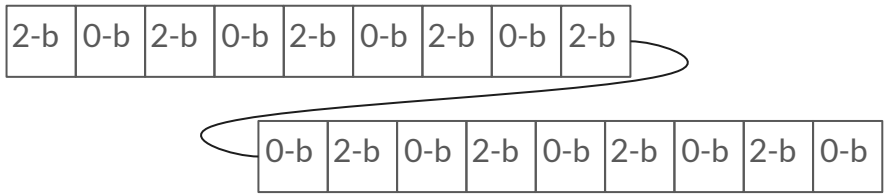
Rossi et al., 2016
Dutt et al., 2014

Goal: Test working memory

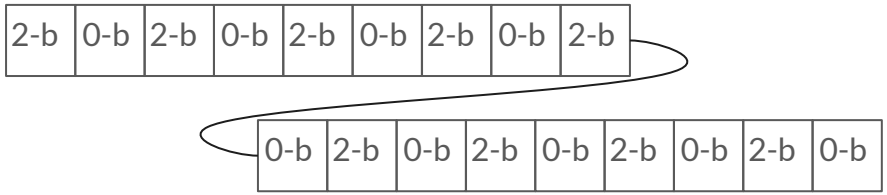


Example 2-back: “If the letter on the screen is the same as 2 letter before, press the spacebar.”

Untrained task (MRS) - with weekdays



Trained task (TIS) - with letters



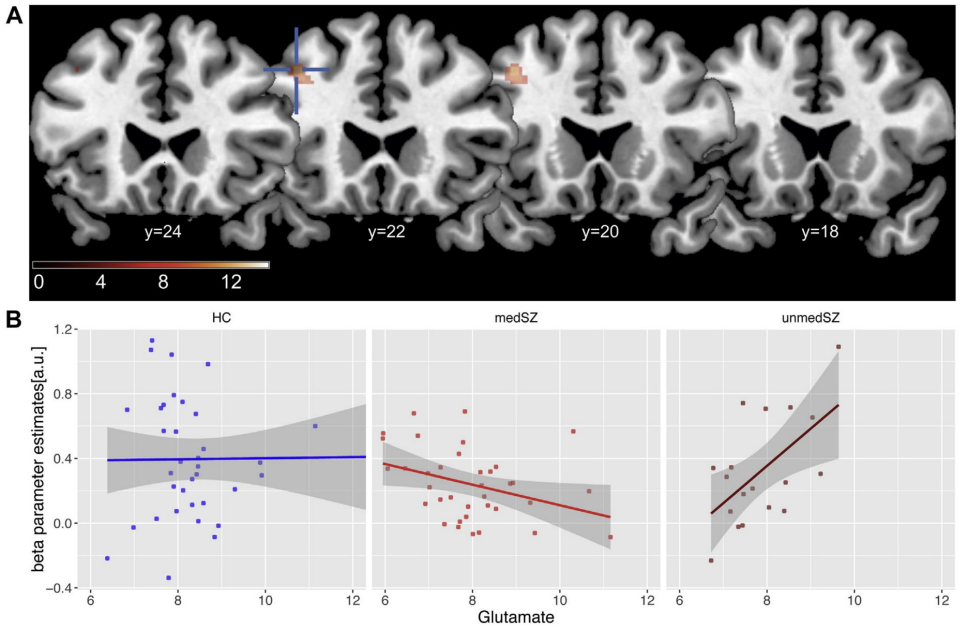
- 18 blocks (48s), 9x 2-back, 9x 0-back
- Compare accuracy and speed of 2-b compared to 0-b.

EPFL

Choosing the N-Back Task

Kaminski et al., 2020
Zhang et al., 2022

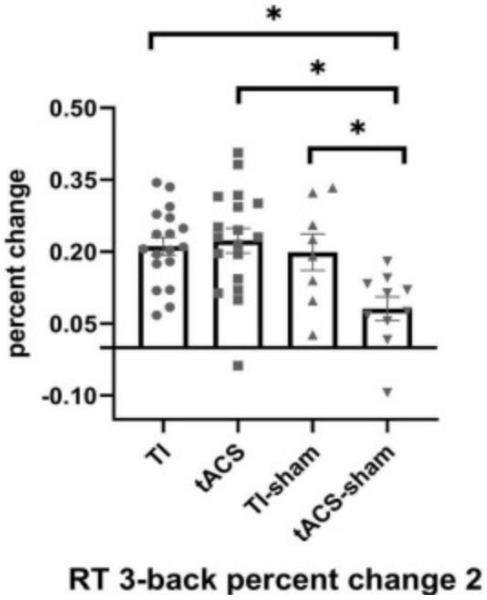
1. N-Back for working memory and glutamate



DLPFC Glutamate correlates with working memory in n-back task for schizophrenia (naïve)

2. N-Back correlates with disease progression and conversion

3. Priming thalamus and DLPFC for TI



Effect of TI on N-back test compared to sham

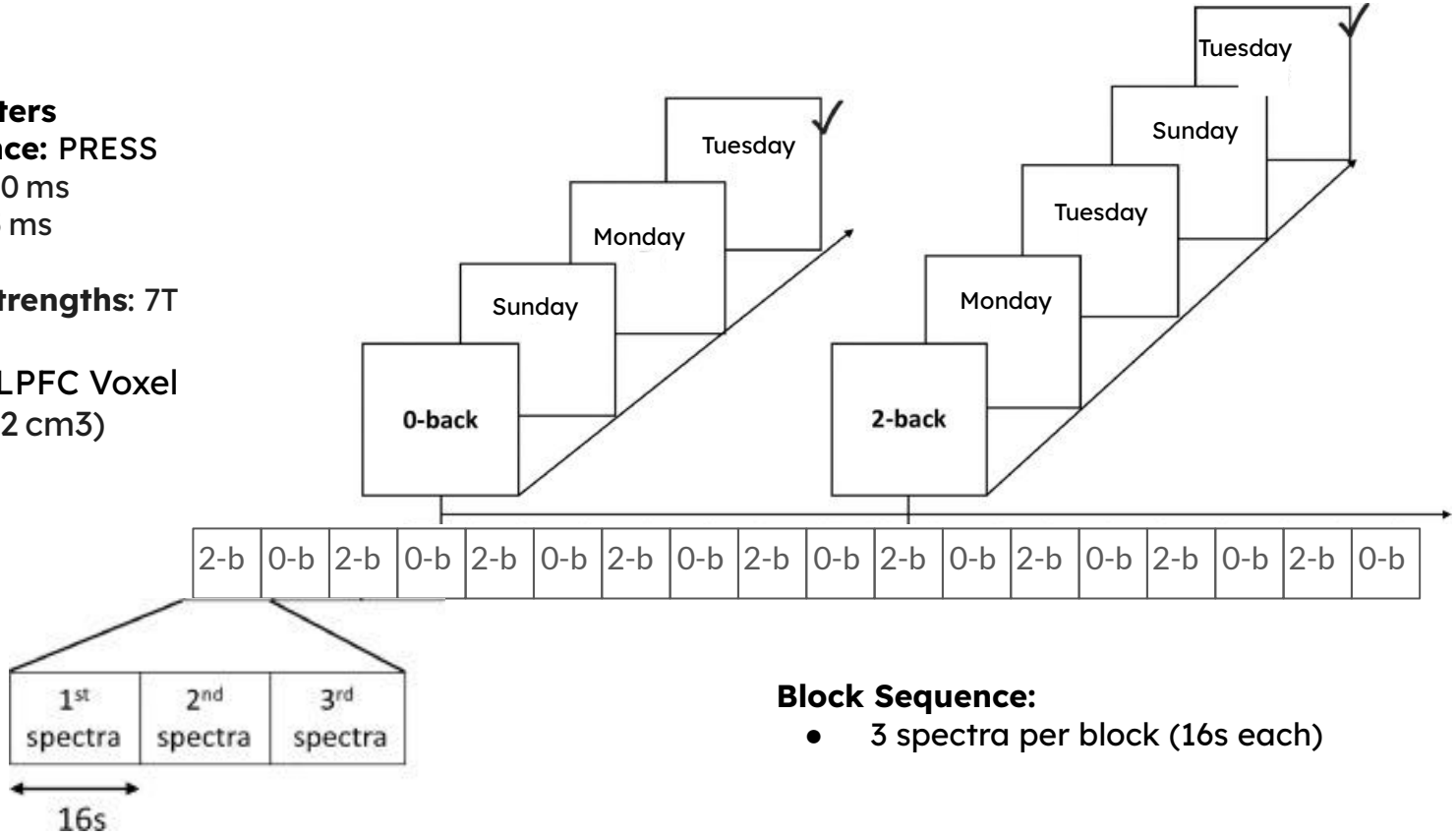
MRS Acquisition

Jelen et al., 2019

MRS Parameters

- **Sequence:** PRESS
- **TR**: 2000 ms
- **TE**: 105 ms
- **NEX**: 8
- **Field Strengths**: 7T

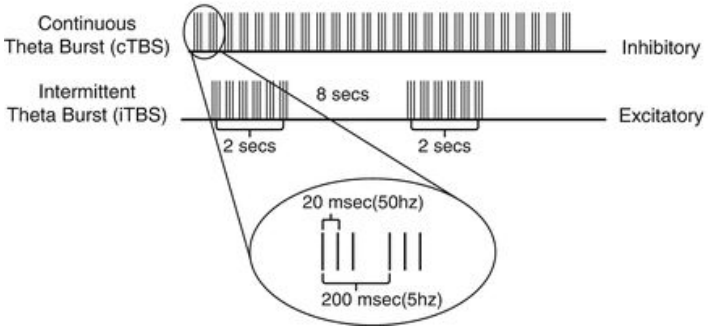
Target left DLPFC Voxel
3 × 2 × 2 cm (12 cm3)

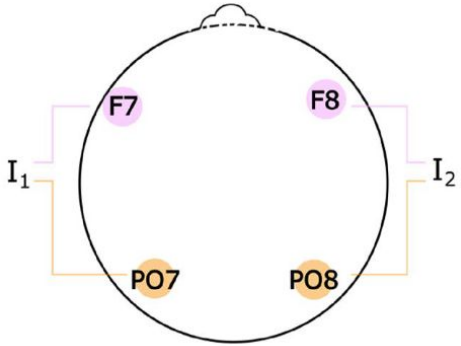


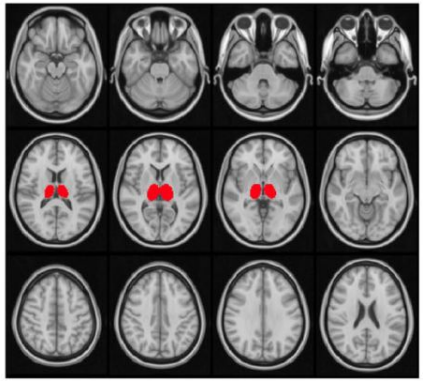
Block Sequence:

- 3 spectra per block (16s each)

tTIS Protocol







- Continuous Theta Burst Stimulation (**cTBS**) => LTD
- β rhythm (Ketz et al.)
- **Bilateral** Thalamus stimulation
- Electrodes: **F7-PO7** and **F8-PO8**
- Amplitude 1-2mA
- FEM for intensity and coverage
- Duration: ~20 min

Grossman et al. 2017, von Conta et al. 2021, floridatmsclinic.com

Expected Results

Physiological

- Reduced Glutamate levels in DLPFC in active group (MRS)
- Diminished brain and GM volume loss in the Thalamus and DLPFC (Pilowsky et al. 2006)

Behavioural

- Improvement in Working Memory in active group - measured through task performance
- Reduction of conversion into Psychotic Disorders (CAARMS & PANSS)

Risks and Limitations

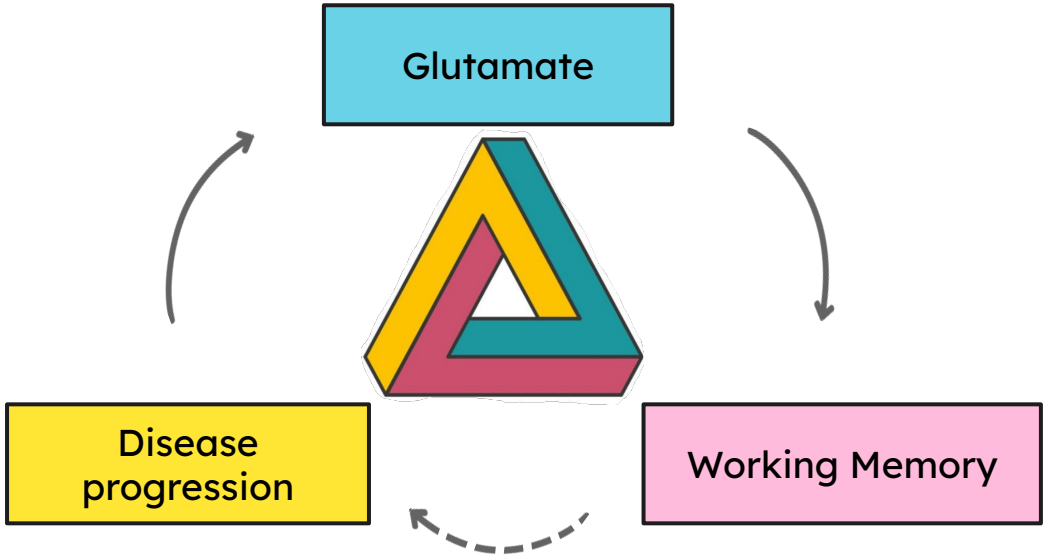
Risks

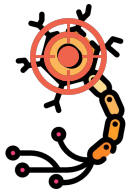
- Epileptic episode
- Well being of patients during experiment
- TI stimulation considered safe (Vassiliadis et al. 2024)
- No contraindications for MRS in UHR

Limitations

- One possible mechanism to explain UHR pathology, one of many regions involved in SCZ
- NMDA receptor hypofunction may be lateralized; left hippocampus (Pilowsky et al. 2006)
- MRS limitations: difficulty to reproduce results (spatial resolution, intra subject variability)

Conclusion and Outlook





Additional slides

For those who want more...

CAARMS Defined UHR

Three UHR groups

- Attenuated psychosis group:
  - Severity and frequency of content, hallucination, disorganized speech
- BLIPS group:
  - Acute phases of less than one week
- Genetic risk group:
  - Psychosis history in first degree relative
  - Change in functioning

	p-value	Estimated hazard ratio†
Thought content	0.16	1.36
Perceptual abnormalities	0.32	1.38
Conceptual disorganization	0.73	0.94
Motor changes	0.41	1.12
Concentration and attention	0.0009	1.54
Emotion and affect	0.016	1.34
Impaired energy	0.013	1.34
Impaired tolerance to normal stress	0.019	1.28
Positive symptoms	0.42	1.28
Negative symptoms	0.0002	1.83
Overall score	0.002	2.16

†A hazard ratio >1 means that risk of onset increases as score increases.

Jung et al. 2005,

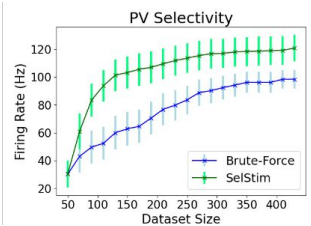
PANSS

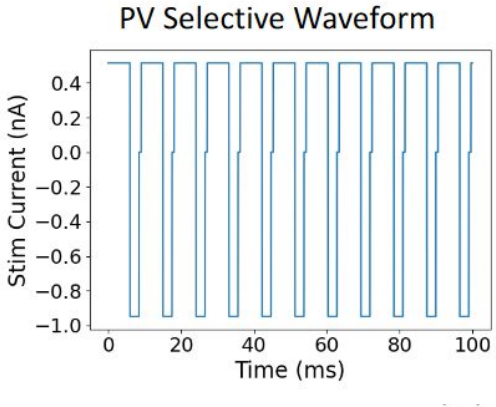
		absent	minimal	mild	moderate	moderate severe	severe	extreme
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganization	1	2	3	4	5	6	7
P3	Hallucinatory behaviou	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7

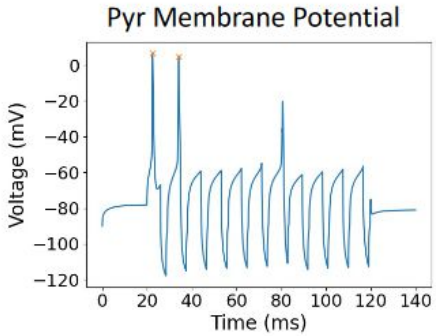
G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorentation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgement & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

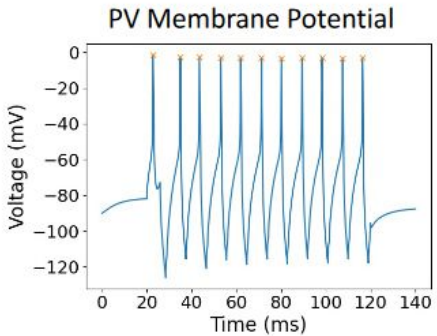
reference.medscape.com, fr.scribd.com

PV neuron specific stim









- TI acts at the network level, ie. in isolated neurons TI has generally no effect
- PV neurons are less active in target than off-target areas, where they are impacted by high freq sinusoids
- Data-driven approach to design cell specific waveforms (MLP)
- Samples waveforms iteratively in data-efficient manner
- For now only validated in computational models. Results prove only data efficiency not selectivity.

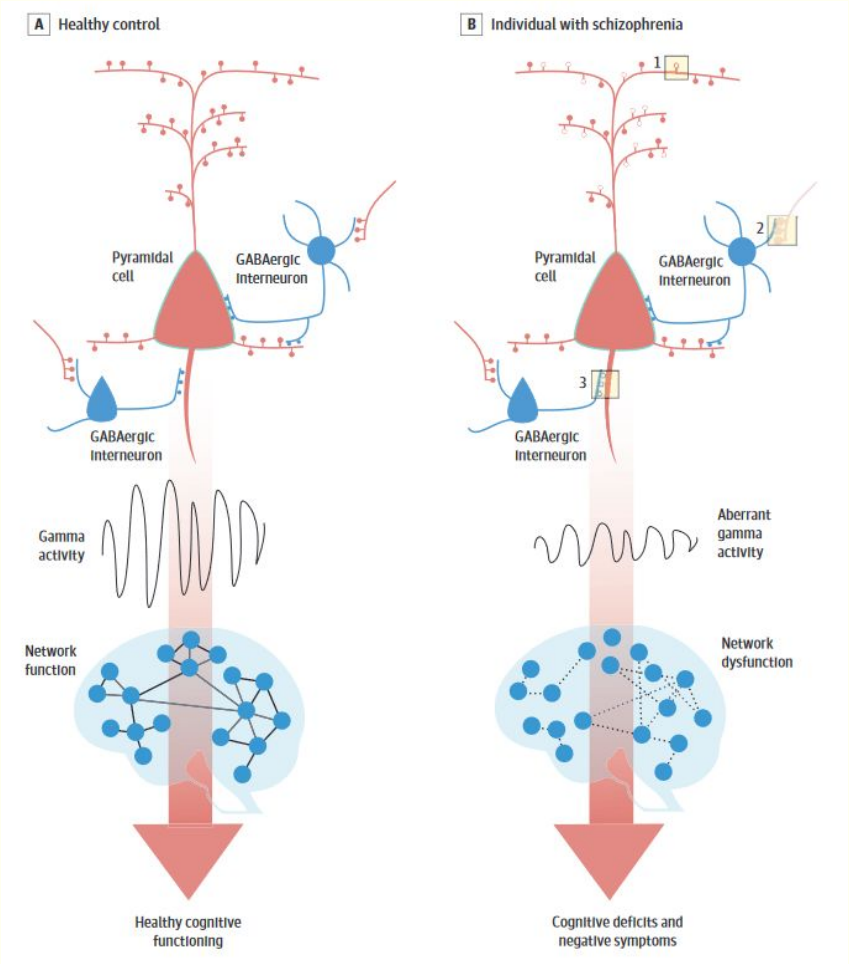
Grover et al. 2024, Goswani et al. 2024

Putative mechanisms

Excitatory cells' output are modulated by GABAergic interneurons - this interplay generates gamma oscillations

In Schizophrenia this mechanism is altered leading to aberrant oscillatory activity:

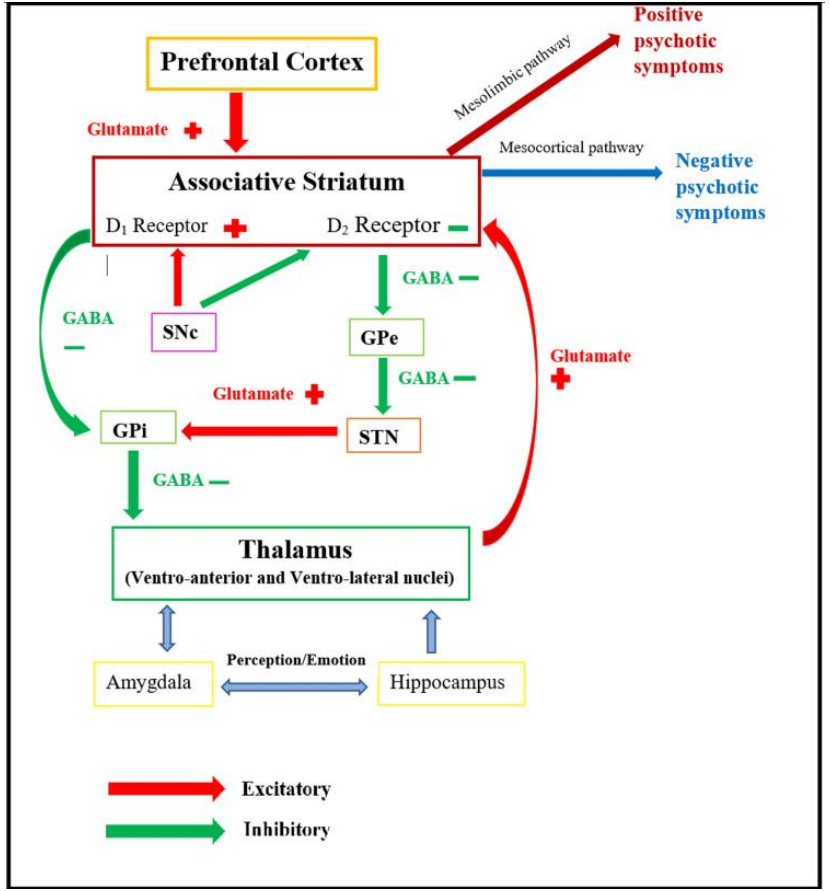
- Loss of pyramidal cell dendritic spines
- Reduced excitatory input to GABAergic interneurons leads
- Reduced interneuron inhibition of pyramidal cells occurs



McCutcheon et al. 2020

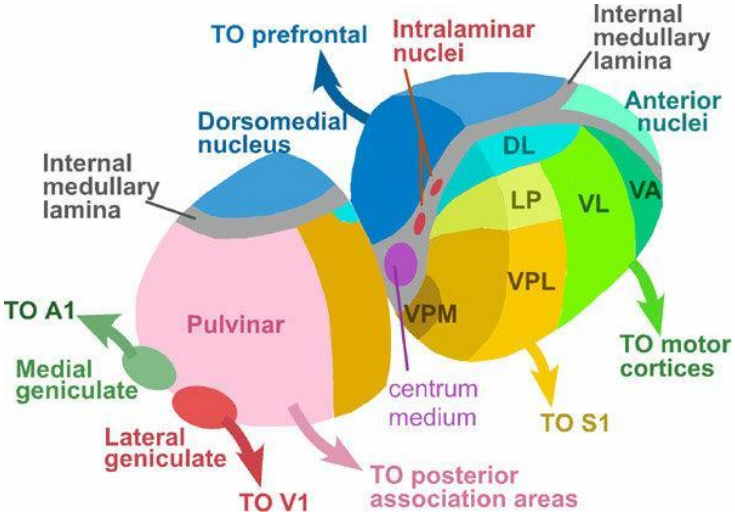
Network of direct and indirect pathways of basal ganglia involved in motor activity and psychotic symptoms

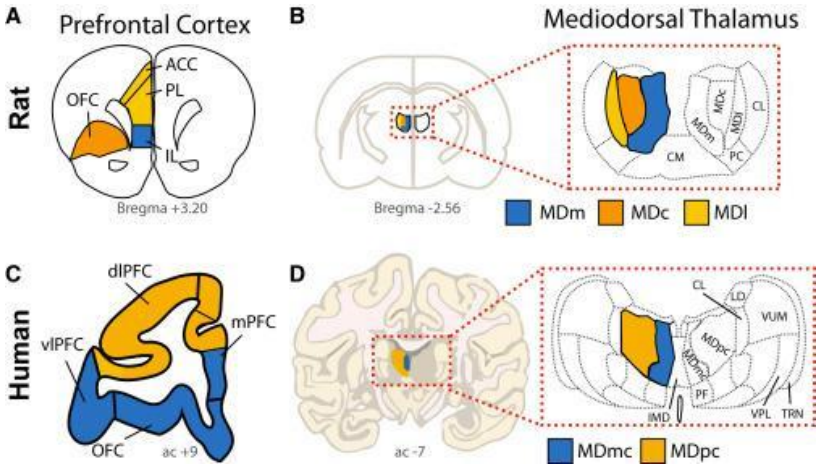
Stimulation and increased activity of excessive D2 receptors in the associative striatum causing schizophrenia.



Luvsannyam et al. 2022

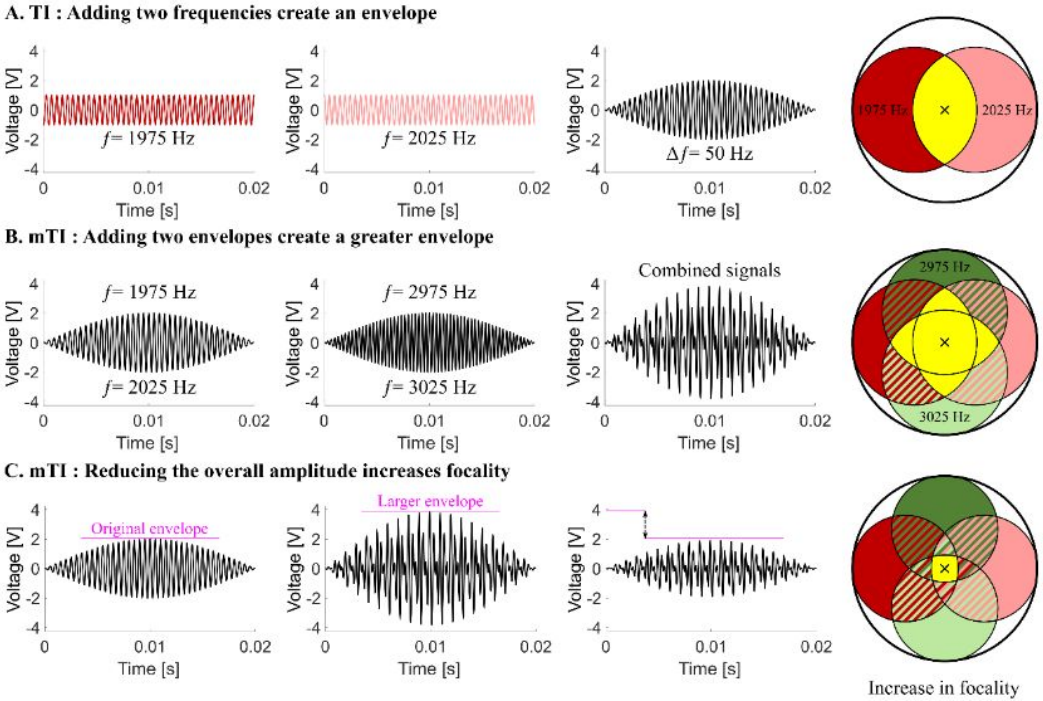
Medial Dorsal Thalamus Parvocellular Nucleus



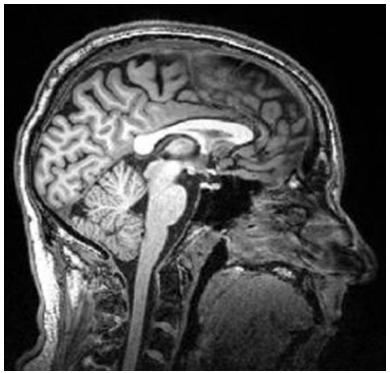


Multipolar TI

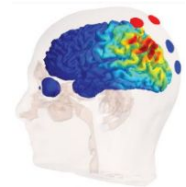
Focal control of non-invasive deep brain stimulation using multipolar temporal interference



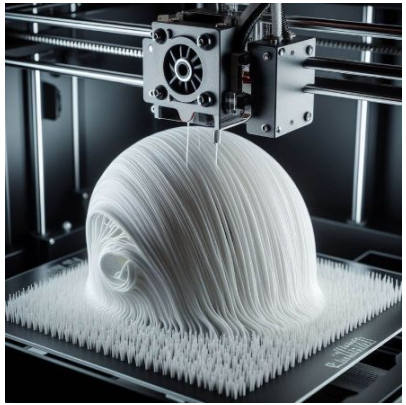
Personalized TI caps



Head Model
w sMRI



Sim4Life

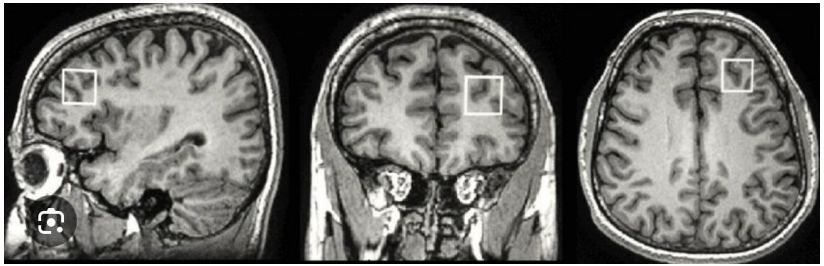


3d printed
Personalized cap

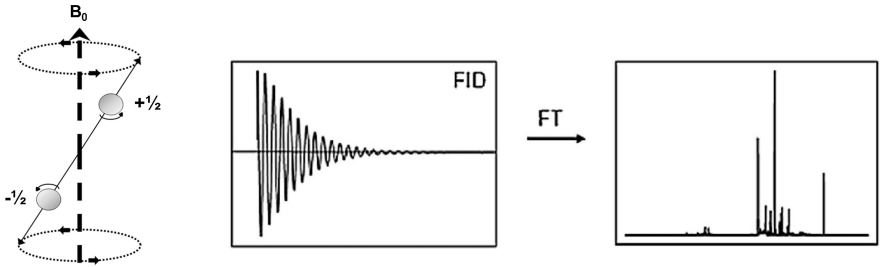
Home based
system

src: Neurobott AG

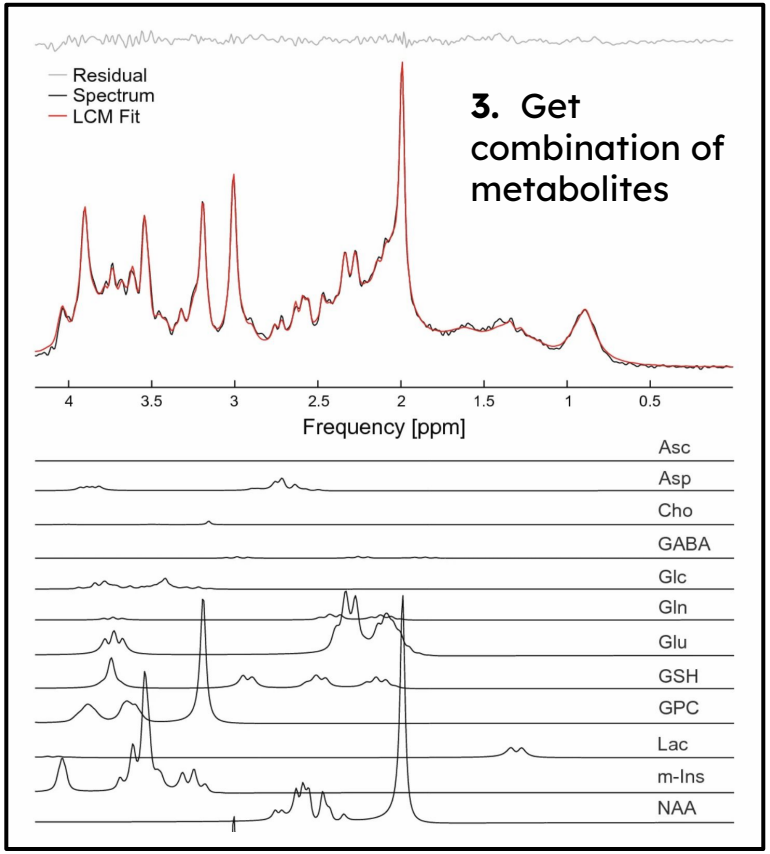
MRS



1. Select Voxel



2. Carry out acquisition



EPFL

Safety of TI in Psychosis

Efficacy of transcranial alternating current stimulation for schizophrenia treatment: A systematic review

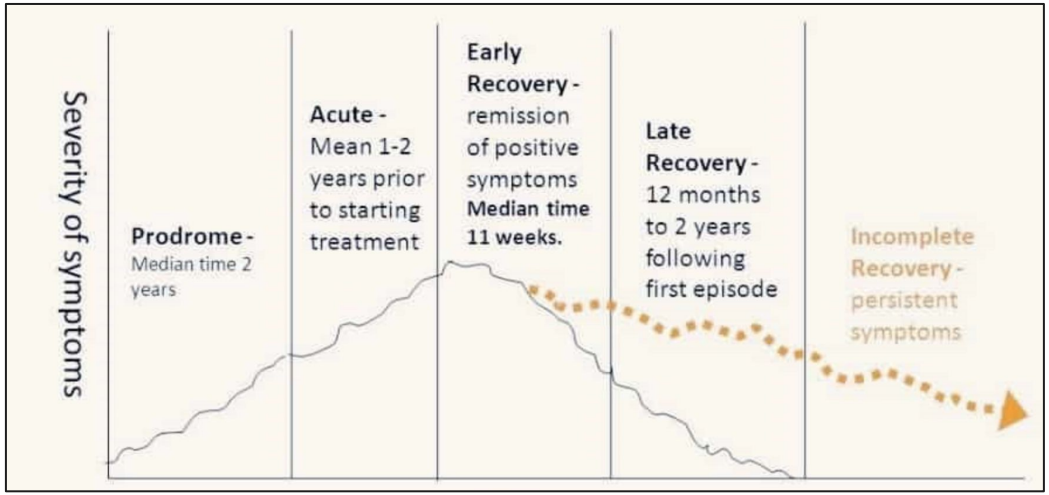
x19 Studies considered it safe

Rong Zhang [a] ✉, Juanjuan Ren [a] ✉, Chen Zhang [a b] ✉

"These studies also reported that tACS was well tolerated and had no serious adverse effects. And ***mild tingling, itching, scalp pain, and phosphenes*** *are commonly reported side effects."*

Psychosis Phases

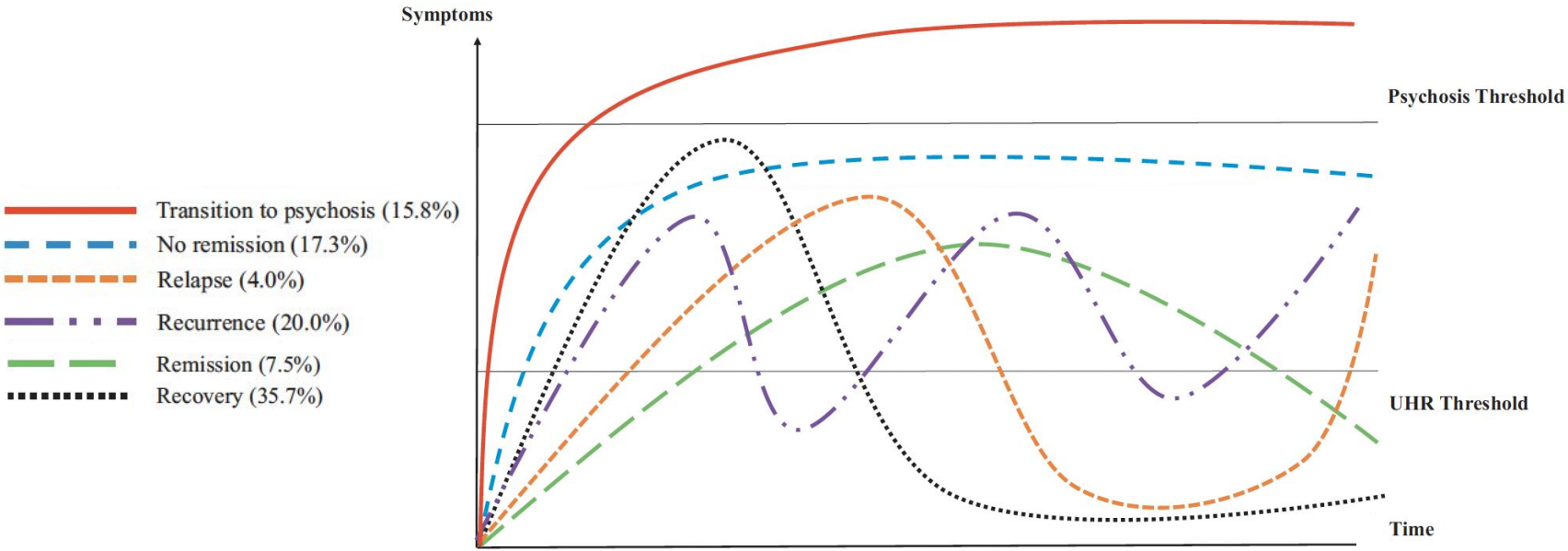
Influence Biomarkers?



Phases of Psychosis Yung (2017)

- Working Memory as primary biomarker for recovery.
- Glutamate as a potential biomarker for psychosis pathogenesis.

UHR Trajectories

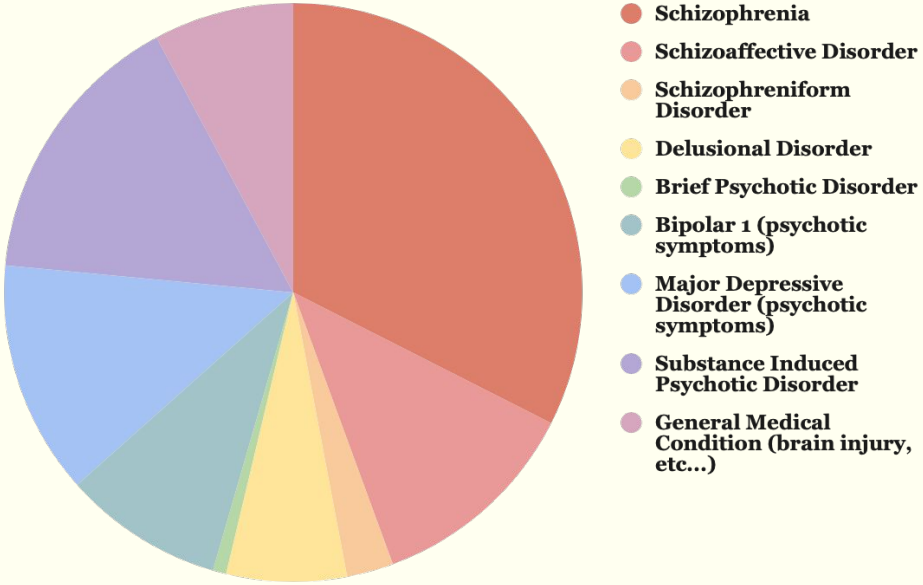


Clinical trajectories in the ultra-high risk for psychosis population Schizophrenia (Andrea Polari, 2018)

Psychosis: a Global Health Issue

Lifetime prevalence of psychosis	3:100
Prevalence of psychosis disorder	1:100
Sex prevalence	Equal

Distribution of Psychotic Disorders



Lifetime prevalence of psychotic disorders in a general population (Jonna Perälä et al. (2007))

Schizophrenia

A differential diagnosis of chronic relapsing psychosis

World Prevalence	1:300
Canadian Prevalence	1:100

56% men

44% women

New diagnosis between 20-34 year old (Canada)	30%

Among this group rate of onset is **2x** higher for men

Canadian Chronic Disease Surveillance System (2019)

Three Phases of Psychosis

1

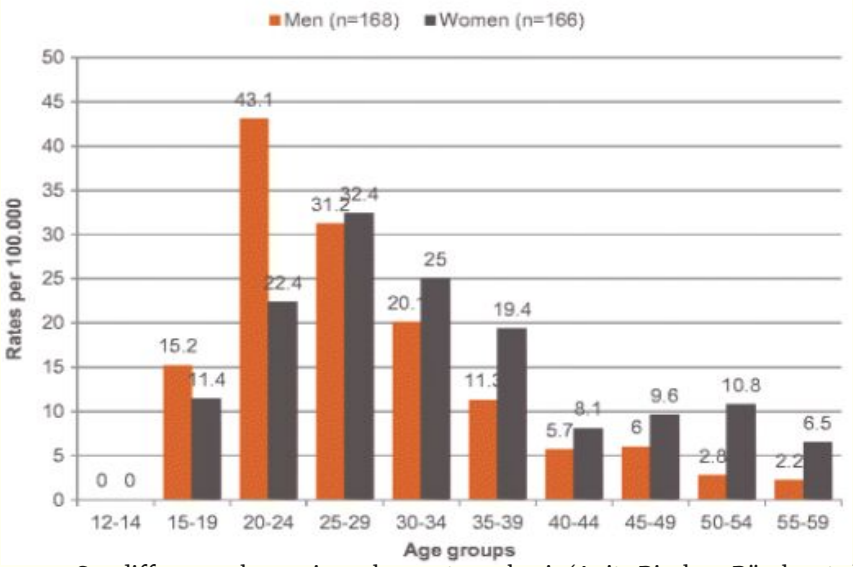
Prodromal Phase:
Sleep disturbance, disorganized thoughts, social withdrawal, suspiciousness, anxiousness...

2

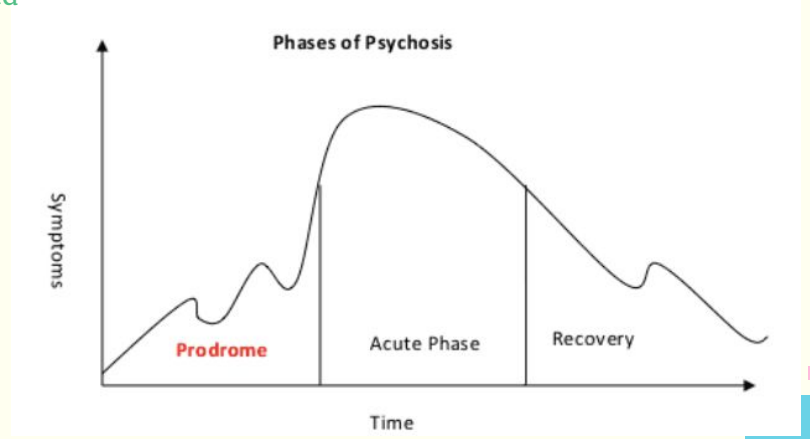
Acute Phase:
Experience of positive symptoms: hallucinations, delusions and disorganized thinking.

3

Recovery:
Positive symptoms tame down but may not leave entirely depending on patient's disease trajectory.



Sex differences by age in early onset psychosis (Anita Riecher-Rössler et al. 2018)

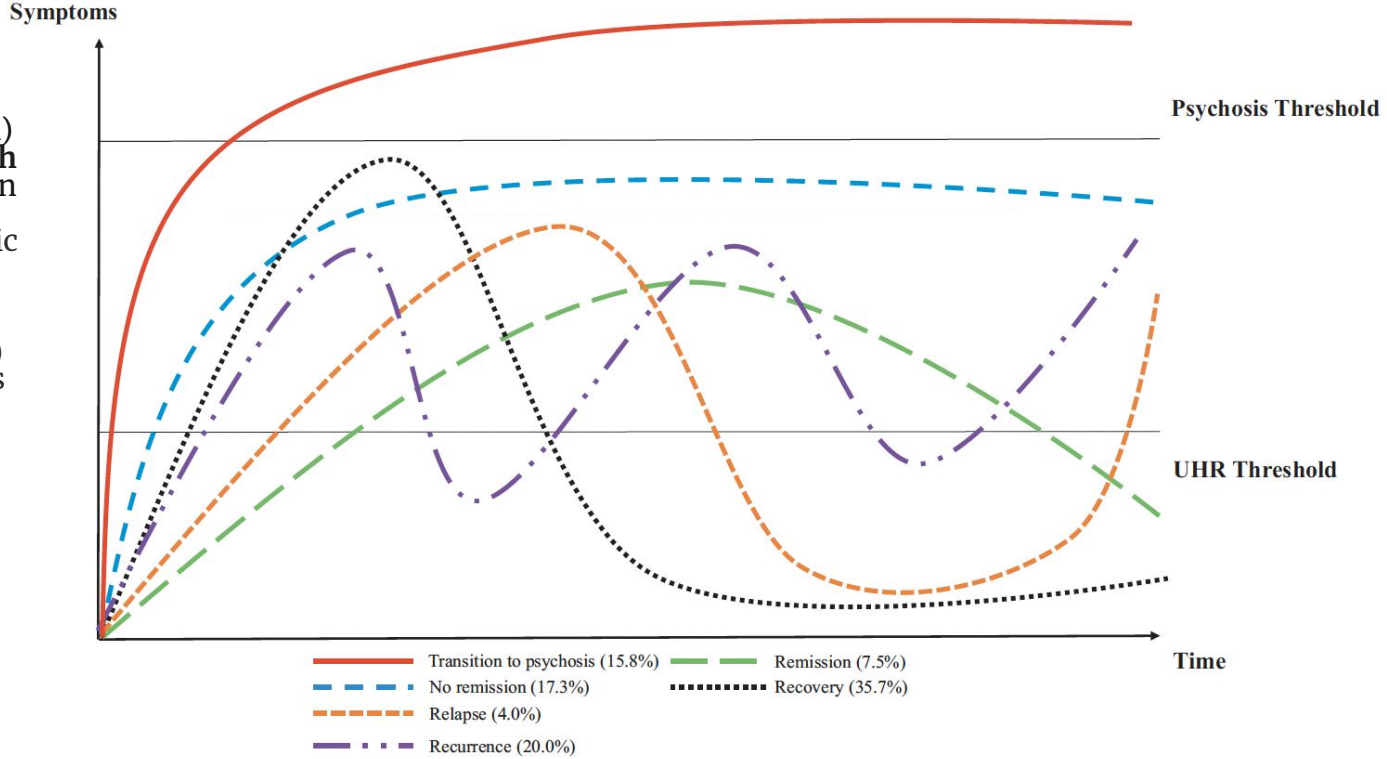


(Early Psychosis Intervention Canada)

Phase Conversions From UHR to Psychosis

Clinical High Risk (CHR) involves one of three **Ultra-High Risk** (UHR) criteria as defined in the DSM-5:

- Attenuated psychotic symptoms
- Full-blown psychotic symptoms that are brief and self-limiting (BLIPS)
- Genetic risk for psychosis



Clinical trajectories in the ultra-high risk for psychosis population Schizophrenia (Andrea Polari, 2018)

Prevention and Treatment

A **Untreated Psychosis**

How soon we administer antipsychotics matters.

Lieberman et al. (2019)

B **Duration of treatments**

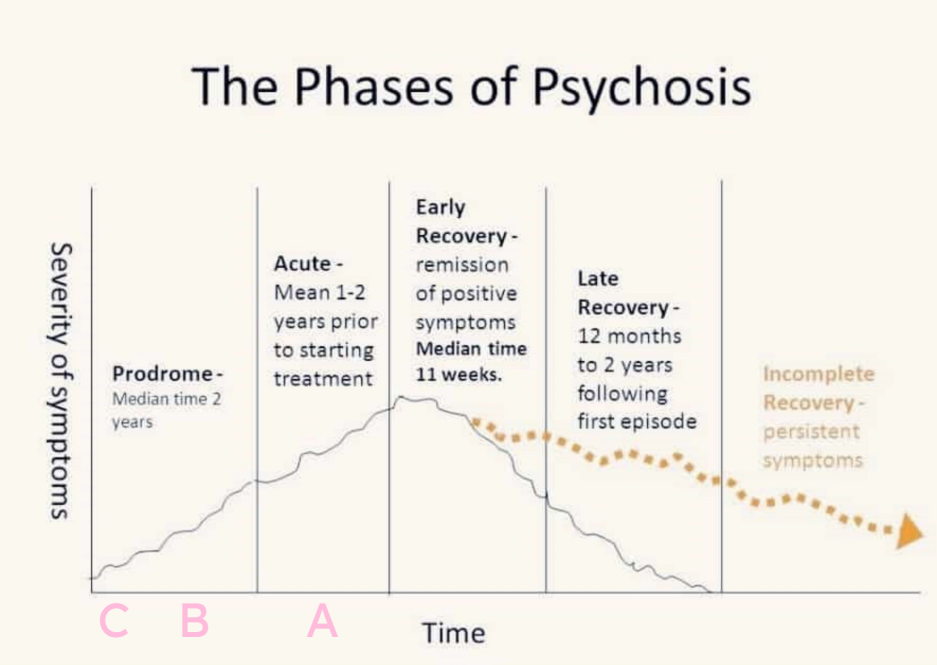
Some programs stop after 1-2 years as symptoms start to recede (too soon)

Lieberman et al. (2019)

C **UHR Preventative Treatments**

Use of low-dose antipsychotics, CBT, integrated family therapy, social skills training...

Yung (2017)



Phases of Psychosis

What biomarkers do we have to detect early onset psychosis?

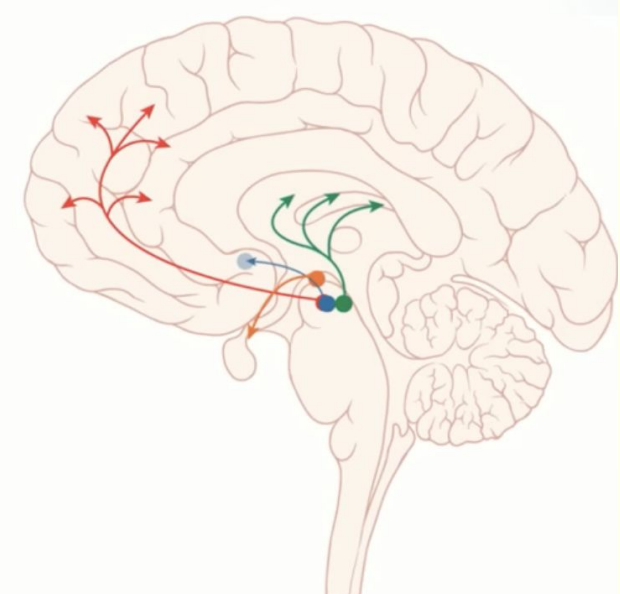
Several Major Mechanisms: The Dopaminergic Model

Mesolimbic Pathway

Hyperfunction VTA to NA is suggested to affect positive symptoms.

Mesocortical Pathway

Hypofunction VTA to prefrontal cortex (DLPFC and VMPFC) is suggested to affect negative symptoms.



D2 Agonist (antipsychotics) reduce positive symptoms of schizophrenia

Summary

- Background: Schizophrenia, pathology ✅, WM deficits ✅ (strong predictor of Psychotic episodes - source??) & other symptoms
- Brain area: Thalamus and DLPFC ✅
  - PV neurons ✅
    - Emit too much glut - glut EXCTTXCT ✅
    - Relationship to pyramidal neurons - suffer glut excitotox ✅
    - Pathological Network (disruption) ✅
- MRS - explain tech ✅
- Ti - explain tech ✅
  - Theta burst stim ???? NOPE ❌
- Hypotheses : stim Thalamus ✅ -> Glut downreg ✅, symptoms ???, task ???
  - Innovation : prevention episodes psychose, TI on Thalamus
- Timeline of the study ✅
  - MRI début pour stim params
  - Duration ??
  - call - back later for determination of schizophrenia
- Stimulation strategy - MRS and TI in our experiment
  - Pairing of both ???? _> Not sure how uch we need to pair them in the end?
  - Frequency MRS ??? ✅
  - Unilateral MRS - justify choice of side ???? ✅
  - Bilateral TI- 20 hz, pairing with the task ???
- Task - N back
  - Evaluation of task performance ??? apprentissage et frequence ???
- Cohort : FES ✅
  - Drug naive ✅
  - Check later if dev into schi ✅
  - N = 200 ✅
  - Multisite ✅
- Condition:
  - Age matched controls ✅
  - FES w stim ✅