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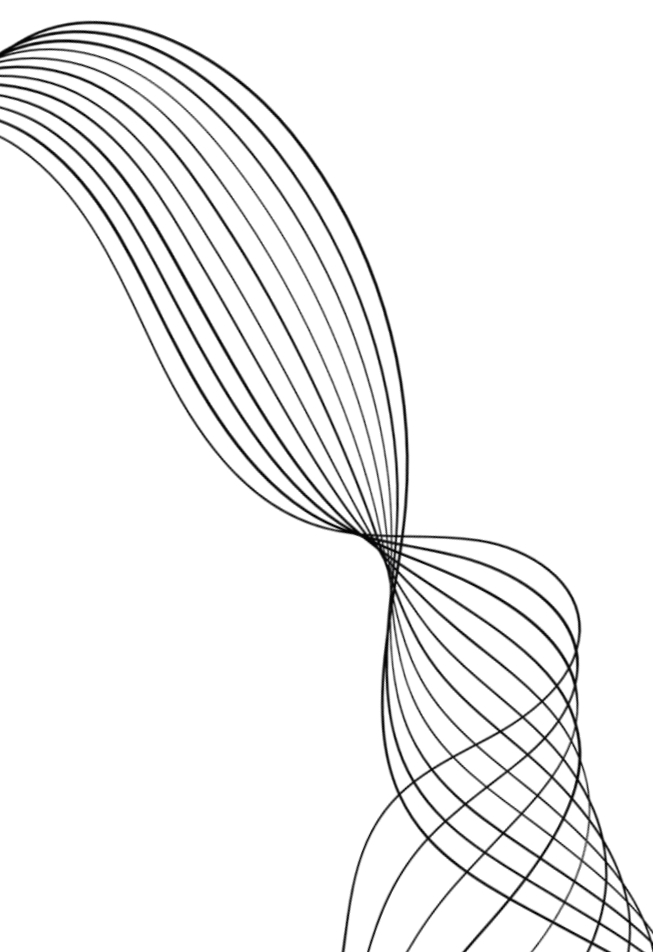
**EEG CORRELATES OF KETAMINE-  
INDUCED DISSOCIATIVE STATE  
IN TREATMENT RESISTANT  
DEPRESSION**

*Alessandra Cinti - PhD Student*





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  - 02 A BRIEF HISTORY OF KETAMINE IN DEPRESSION
  - 03 EEG CORRELATES OF KETAMINE IN TRD
  - 04 KETAMINE-INDUCED DISSOCIATIVE STATE
  - 05 REASEARCH STUDY

# 01. PHARMACOLOGICAL TREATMENT IN DEPRESSION SO FAR



**Depression** remain a **leading cause of disability** world-wide (WHO,2017)



Current depression treatments have limitations:

- delayed onset
- inadequate response for up to a third of patients



Many patients develop persistent, **treatment-resistant depression (TRD)** (Al-Harbi, 2012).

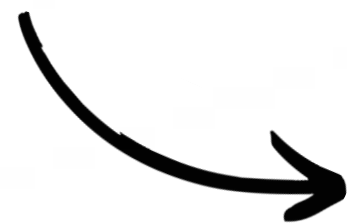
## 02. A BRIEF HISTORY OF KETAMINE IN DEPRESSION

### First Evidence (Berman et al.)

Subanesthetic IV Ketamine (0.5 mg/kg) infused over 40 minutes in 8 medication-free patients with MDD and BD

**Rapid and Sustained Antidepressant Response**  
evident as soon as 4 hours post-infusion and continued enhancement up to 72 hours

**early 2000**



### First replication study (Zarate et al.)

18 patients with *TRD*

**significant antidepressant effects**  
110 min after the infusion,  
peak after 1 day,  
fading after 1 week

The most common side-effect was  
**acute dissociative symptoms**

**2006**



### Recent meta-analyses (Kishimoto et al., n.234; Wilkinson et al., n.167)

patients with MDD and BD

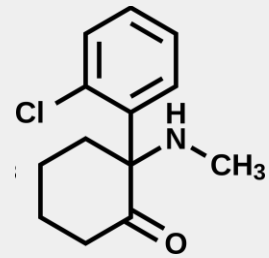
**ketamine reduced depression**  
beginning at 40 min, peaking at day 1  
and losing superiority by days 10–12

**reduced suicidal ideation**  
on both clinician-administered and  
self-report outcome measures,  
lasting up to 1 week

**2016 - 2018**

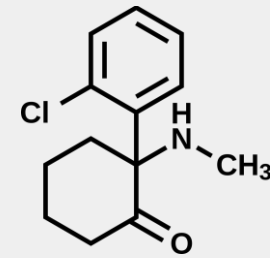
# 03. EEG CORRELATES OF KETAMINE IN TRD

Ketamine induces complex EEG changes in TRD patients



**EEG Patterns** after intravenous (IV) ketamine

- **Decreased** theta and alpha power
- **Reduced** beta power in central-parietal regions
- **Increased** gamma power



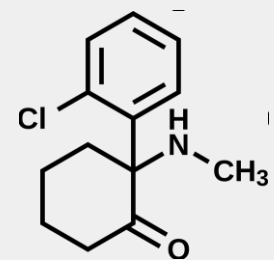
Reduction in **depressive symptoms**

- **Theta** and **gamma** measures were most predictive of early and sustained decrease in **depressive symptoms**
- **Alpha** measures were most predictive of early and sustained decrease in **suicidal ideation symptoms**



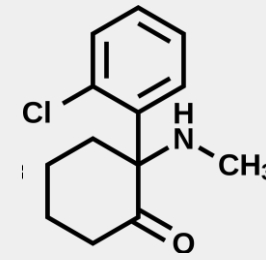
# 04. KETAMINE-INDUCED DISSOCIATIVE STATE

**DISSOCIATION** is a disruption or detachment from one's thoughts, feelings, memories, or identity (DSM-V)  
It has been seen to be **experienced with ketamine**



Mechanism of Ketamine-Induced  
Dissociation:

- Dissociation seems to be mediated by antagonism at the NMDA receptor



Ketamine administration in **healthy controls**:

- **Reduced alpha and beta** connectivity
- **Increased gamma and delta** connectivity
- Relationship between increases in **depersonalization** and **beta** inter-(DMN-SN) and **delta** intra-network (SN) connectivity.

# 05. RESEARCH STUDY

## Objective n° 1

identify **EEG patterns** associated with acute ketamine-induced *dissociation*



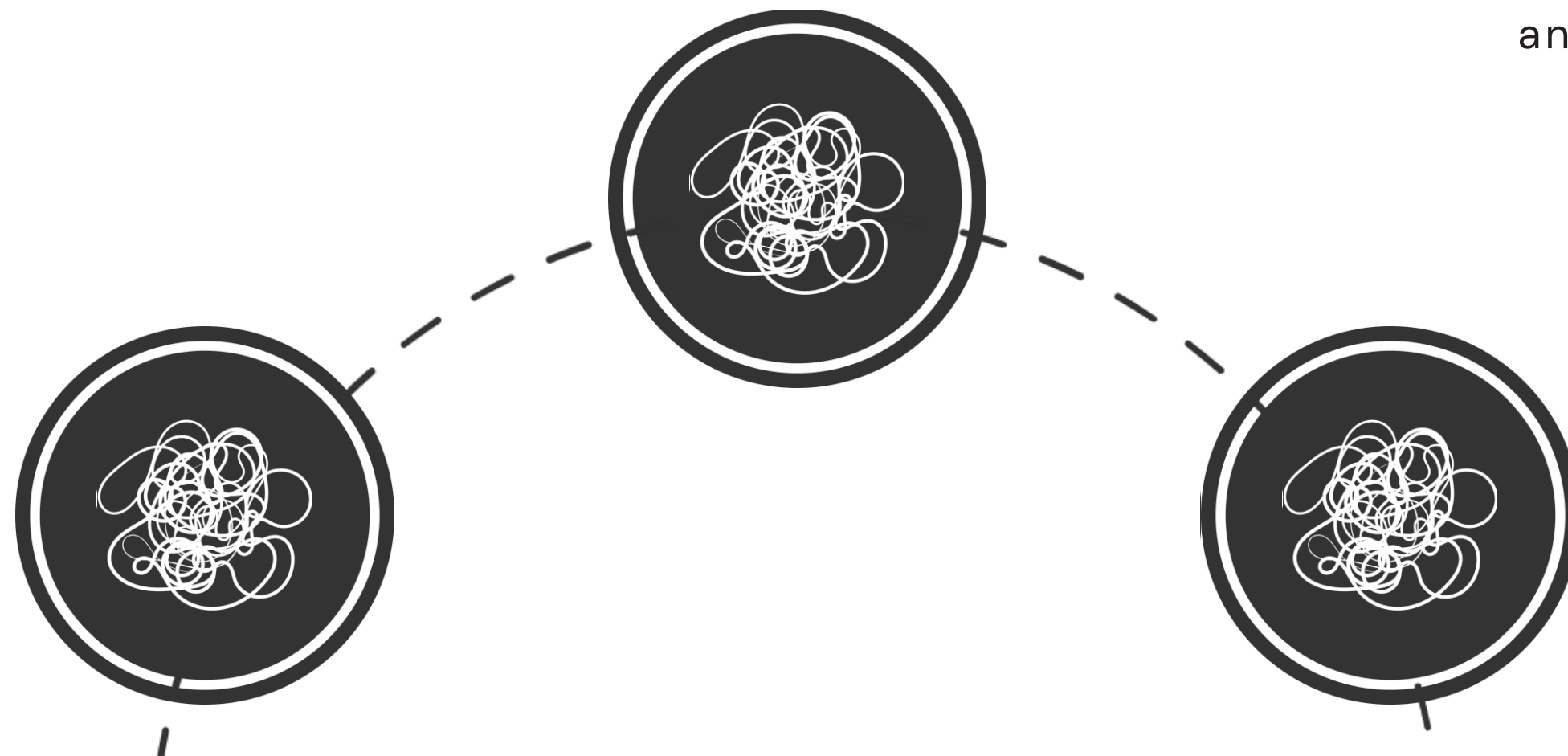
## Objective n° 2

these patterns can be considered as a **neurophysiological marker of TRD**



## Objective n° 3

implementing **novel therapeutics** in order to alleviate symptoms and improve wellbeing in people with unipolar and bipolar depression



# PATIENTS ENROLLED



## Inclusion Criteria:

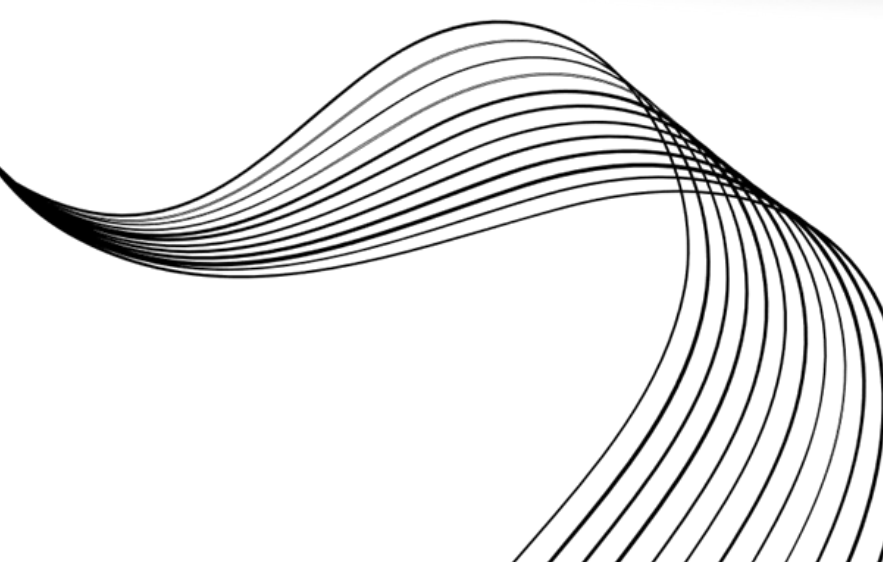
- Diagnosis of MDD or BD with **long-lasting depressive episodes**
- **MADRS > 35**
- Patients have **failed** to respond to **at least 2 trials** of standard therapy;
- ketamine dosage: **0.5–1 mg/kg**;

# EXPERIMENTAL DESIGN



**First 25 patients** with unipolar or bipolar depression from the Psychiatric Department of AOUS Santa Maria alle Scotte, Siena:

	<i>Mean (SD)</i>
<i>Age</i>	52,32 (11,13)
<i>Education</i>	16,12 (3,15)
<i>Dosage</i>	0,925 (0,15)
<i>N° visit</i>	9 (8,4)





# EVALUATION CRITERIA

## EEG CORRELATES

EEG amplifier and montage



Neuroelectrics, Barcelona (Spain)

- **32-channel** Starstim EEG device with 2 additional electrodes over the left mastoid as a reference
- **6 minutes resting-state** recording before and immediately after intravenous (IV) Ketamine

EEG electrodes



## DISSOCIATIVE STATE

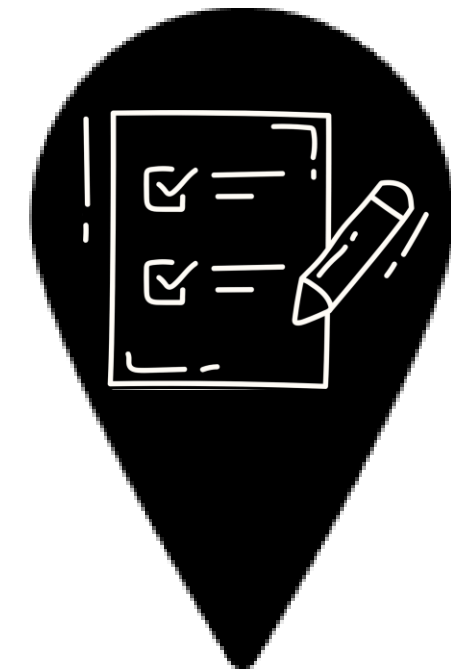
### CADSS - THE CLINICIAN-ADMINISTERED DISSOCIATIVE STATES SCALE

- **27 items**
- 3 subscales
  - AMNESIA**
  - DEPERSONALIZATION**
  - DEREALIZATION**
- score from 0 (absent) to 4 (extreme)

*Bremner, 1998*

# METHODOLOGICAL WORKFLOW

## EXPERIMENTAL DESIGN



pre-infusion  
**EEG recording**

6-minute resting state EEG  
3 minutes Eyes-Open (EO)  
3 minutes Eyes-Closed (EC)

**IV Ketamine  
infusion**

30-minute EEG  
during the infusion

post-infusion  
**EEG recording**

6-minute resting state EEG  
3 minutes Eyes-Open (EO)  
3 minutes Eyes-Closed (EC)

**Clinical  
Assessment**

**CADSS** for dissociative  
state

**MADRS** for depressive  
symptoms

# RESTING-STATE EEG ANALYSIS

EXPERIMENTAL DESIGN

1

## Pre-processing:

1. 1-80 Hz bandpass filtering
2. 48-51 Hz notch filter
3. Semi-automatic artifact removal
4. ICA
5. Re-referencing

2

## Outcomes:

1. **FREQUENCY POWER** (Spectral power analysis - Fast Fourier Transform);
2. **OSCILLATORY POWER** (Irregular Resampling Auto-Spectral Analysis - IRASA);
3. **ENTROPY RATE** (Lempel Ziv Complexity 76 - LZC76 normalized)

# KETAMINE-INDUCED DISSOCIATIVE STATE

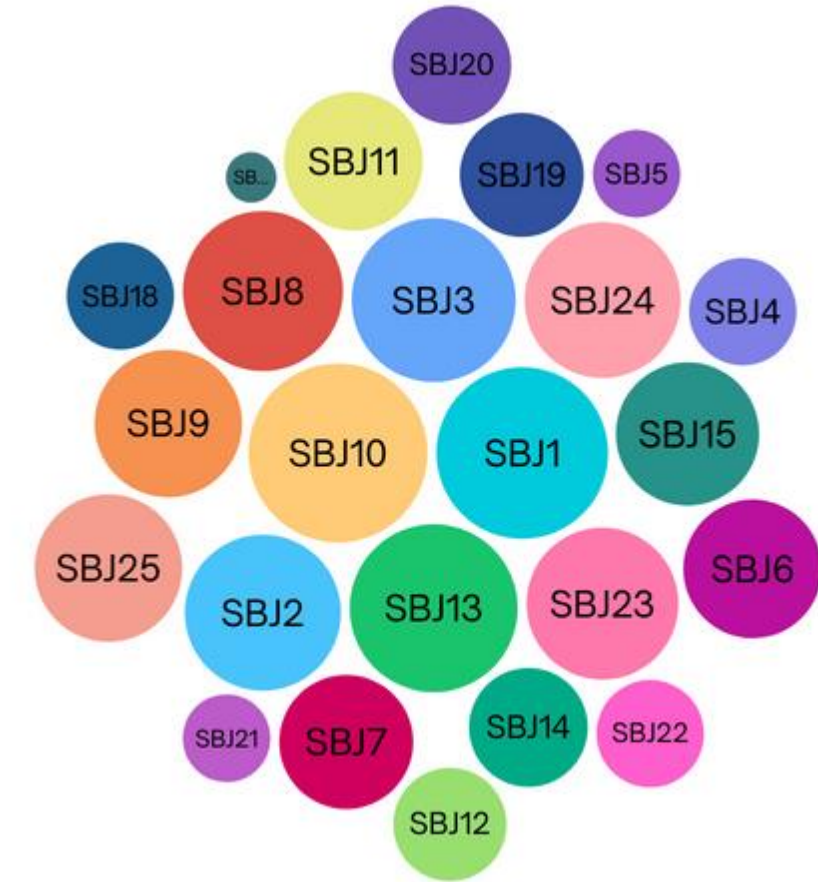
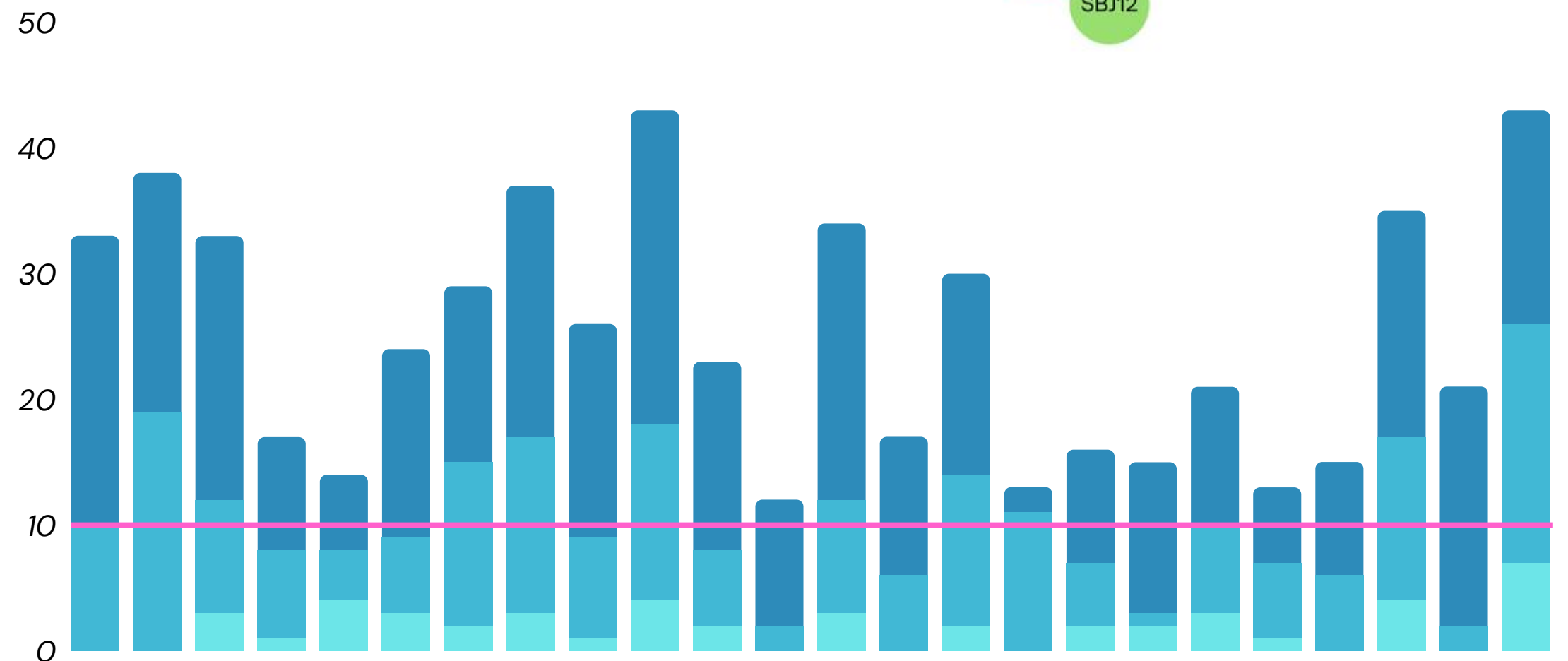
RESULTS

## CADSS SCORE

	Mean (SE)
<b>TOTAL</b>	29,44 (3)
<b>Amnesia</b>	2,2 (0,42)
<b>Depersonalization</b>	9,08 (1,02)
<b>Derealization</b>	15,32 (1,48)

### CADSS scoring:

- 0-10: No dissociation
- 11-20: Mild
- 21-30: Moderate
- > 30: Severe

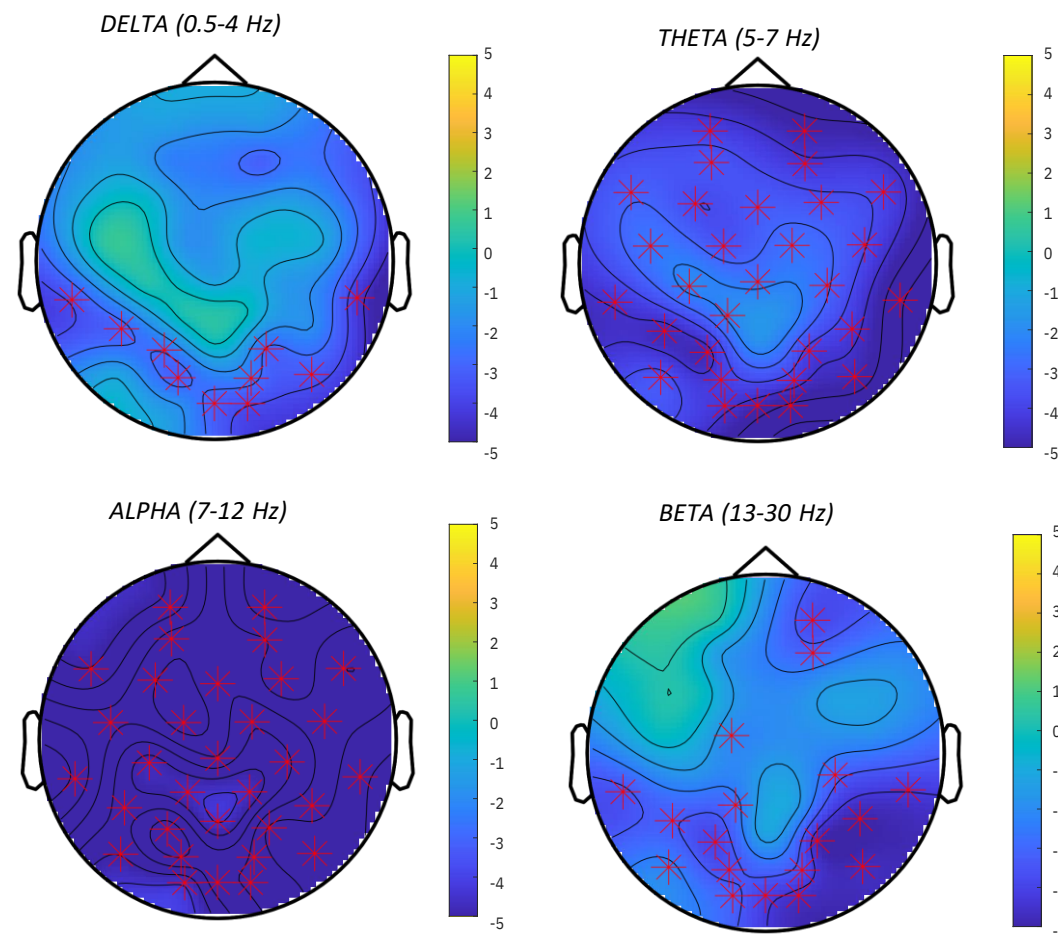
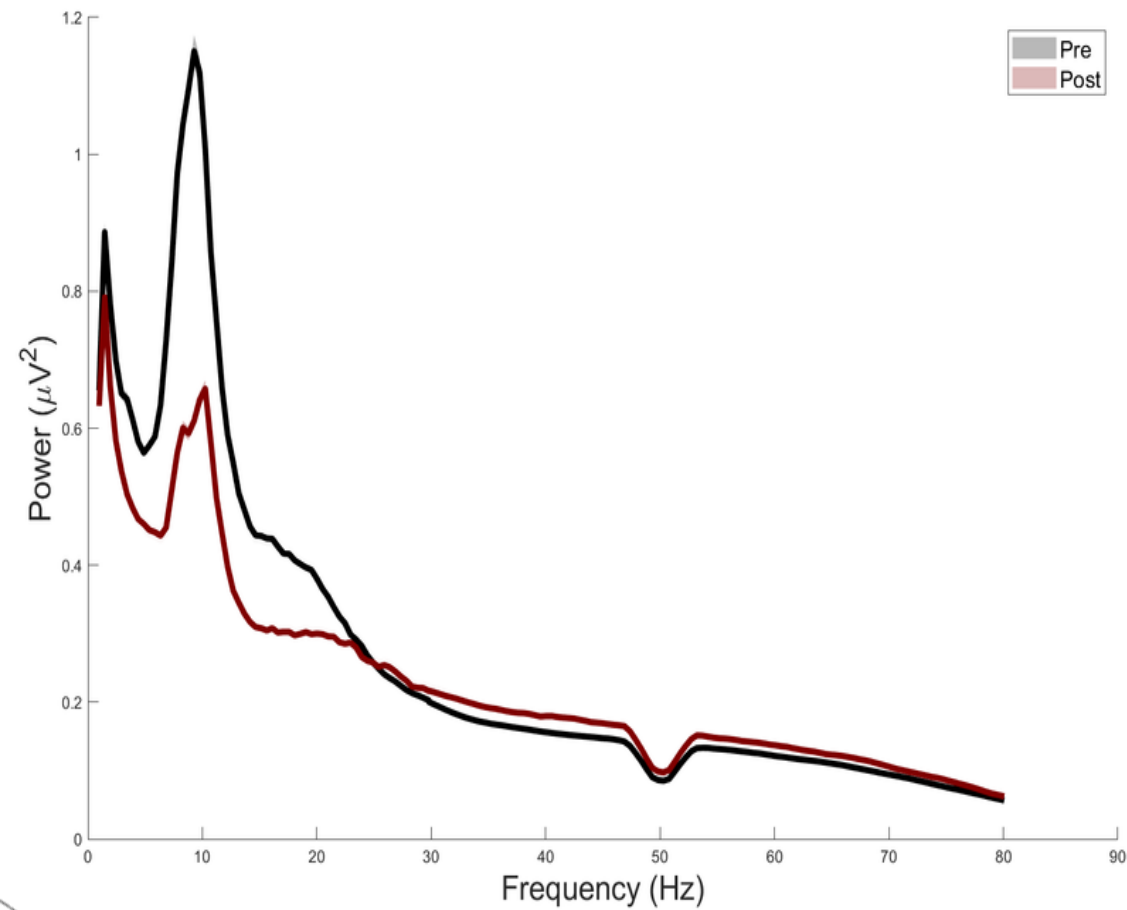




# FREQUENCY POWER CHANGES

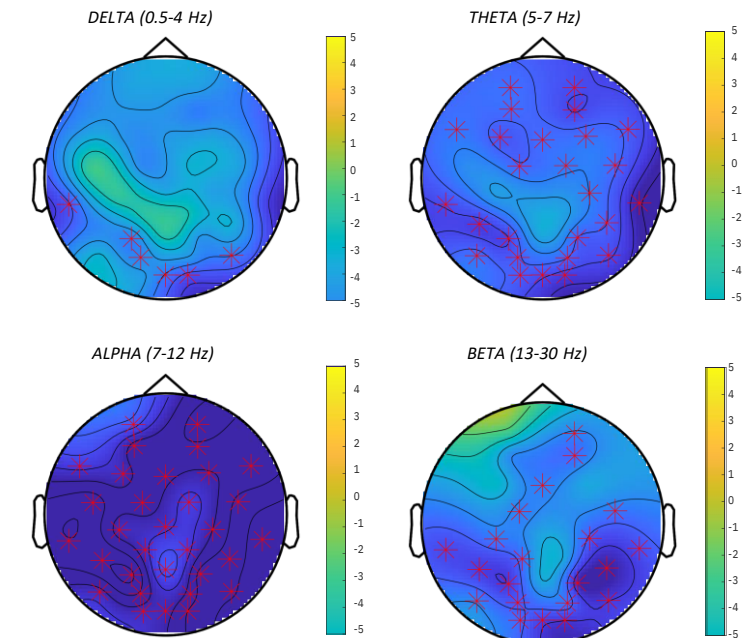
POST vs PRE, Cluster-Based Permutation Analysis (CBP):

- **DECREASE** in Delta, Theta, Alpha, and Beta band

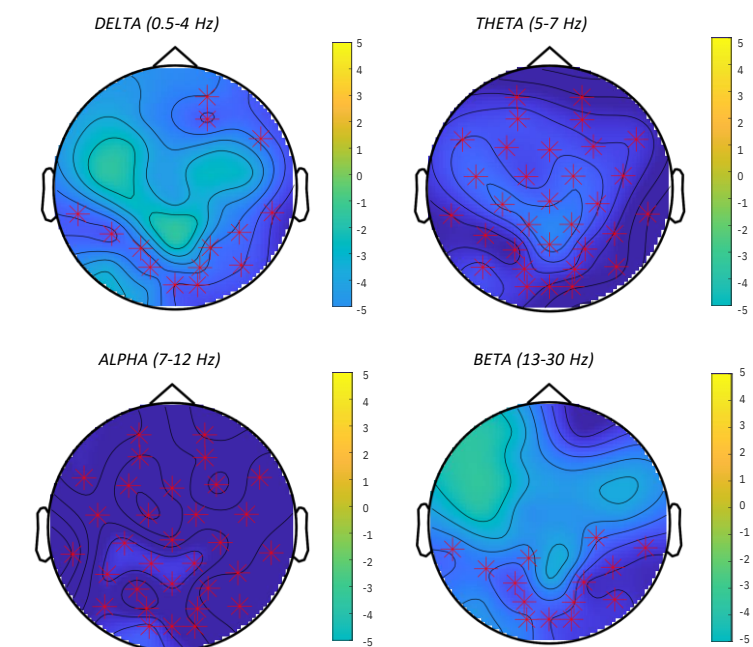


## RESULTS

### EYES-OPEN



### EYES-CLOSED

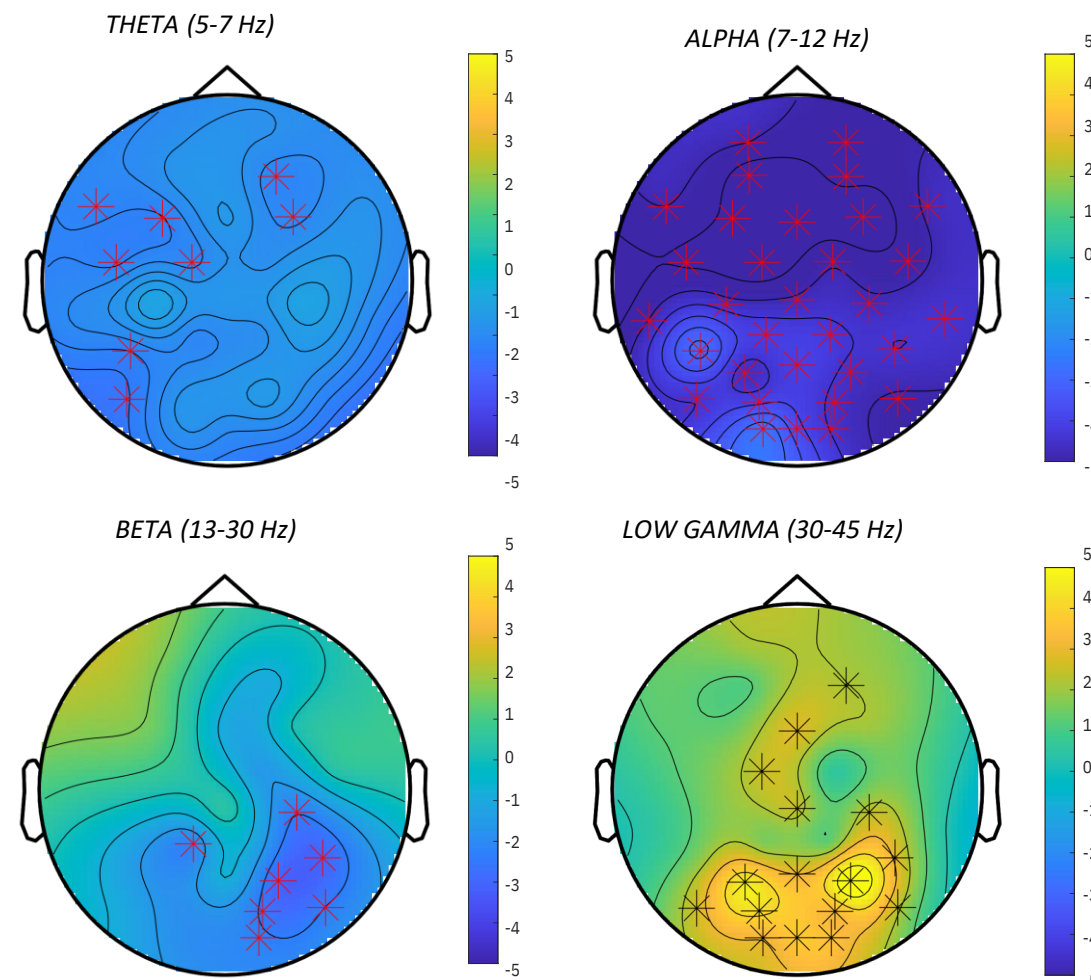
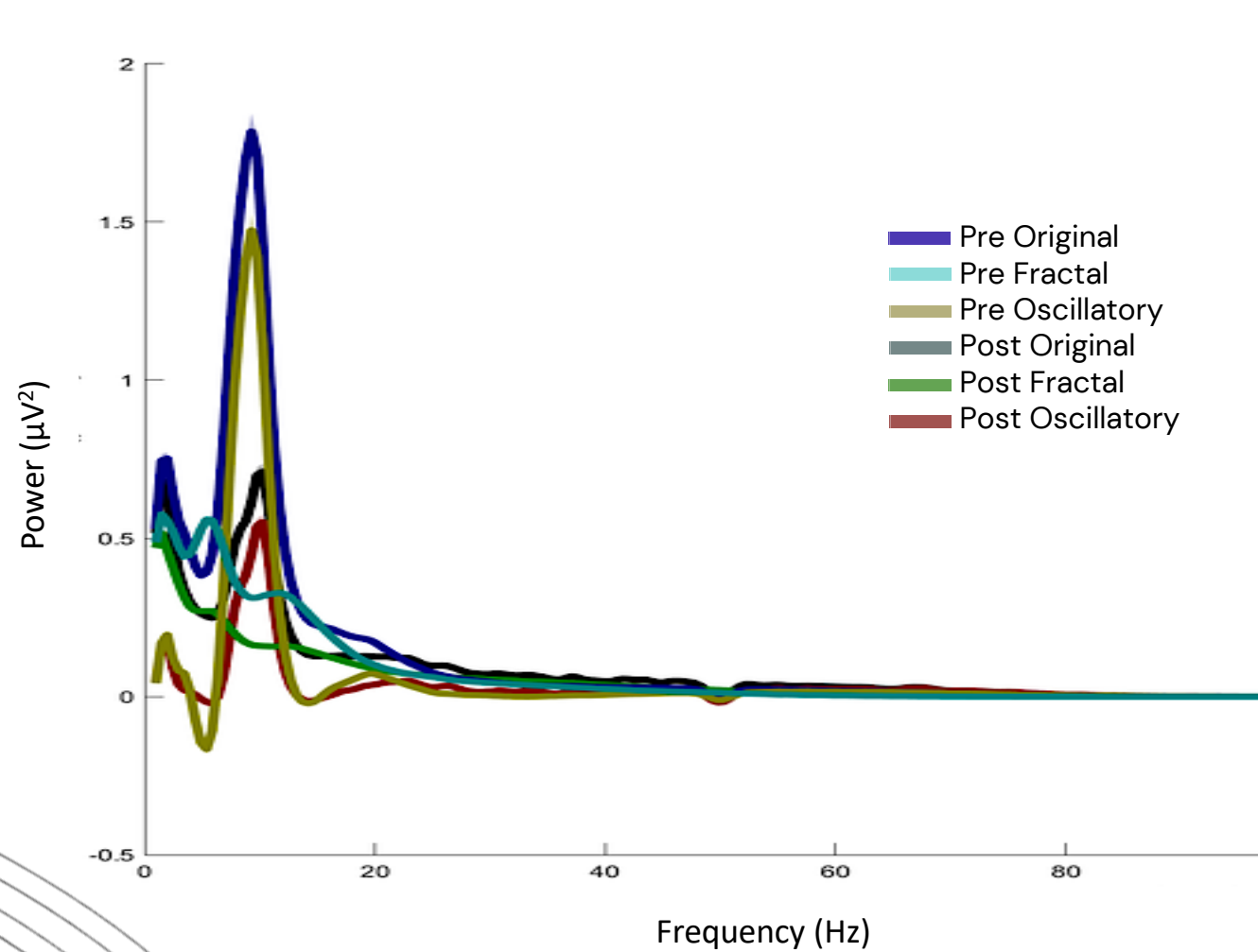




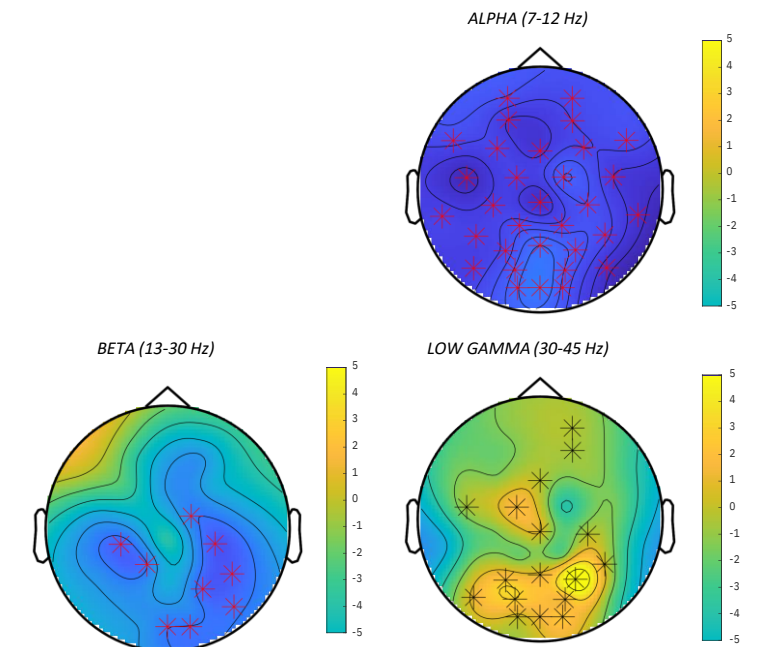
# OSCILLATORY COMPONENT CHANGES

Irregular Resampling Auto-Spectral Analysis (IRASA):

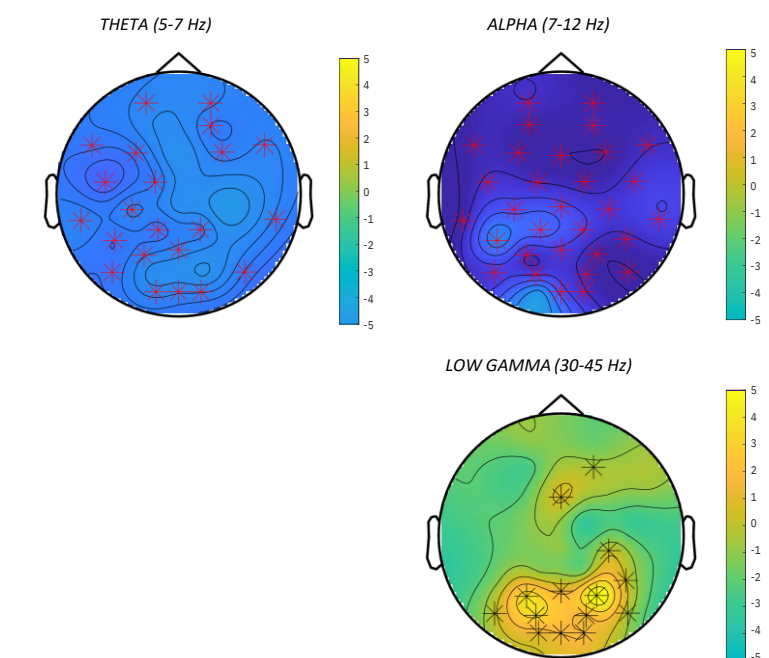
- **DECREASE** in Theta, Alpha, and Beta frequency band
- **INCREASE** in Low Gamma frequency



## EYES-OPEN



## EYES-CLOSED

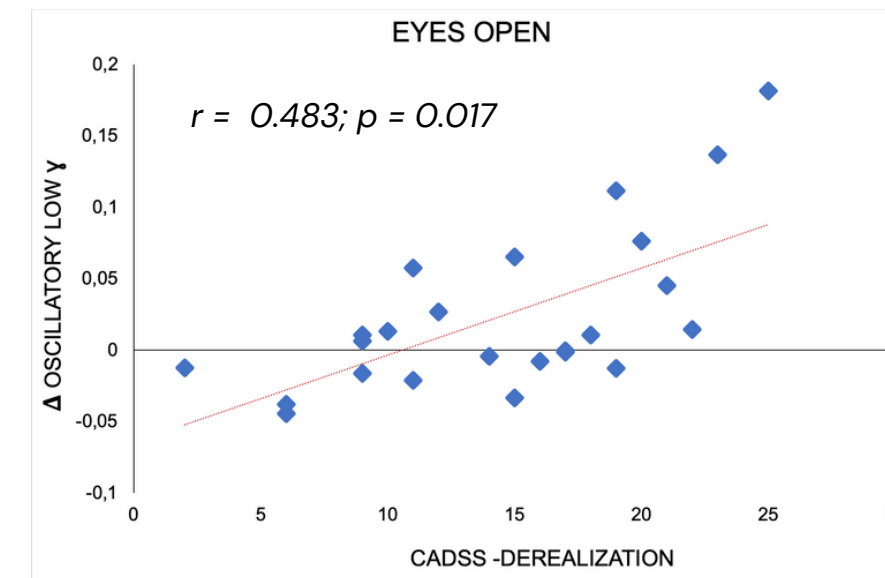
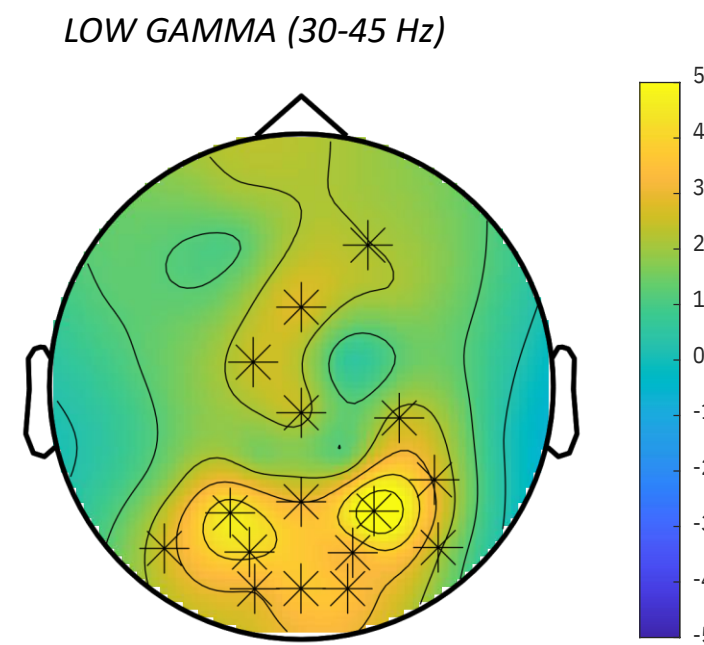
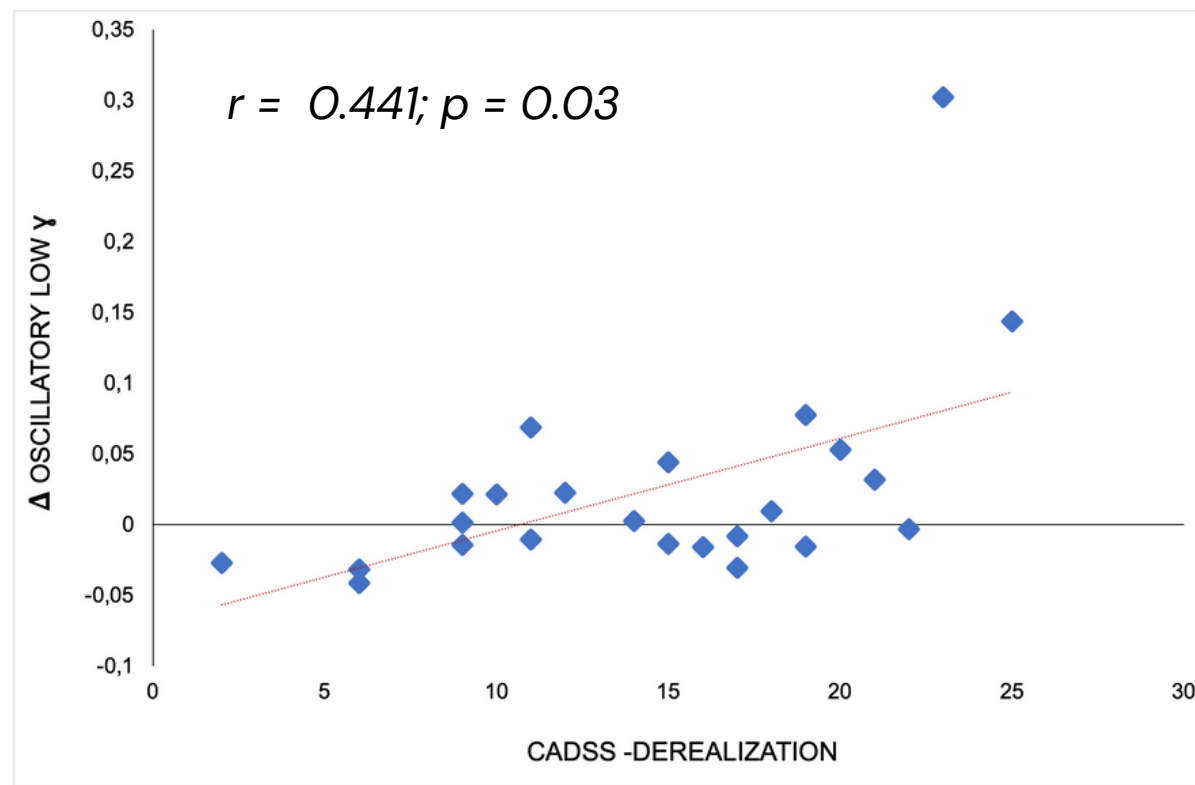


## RESULTS

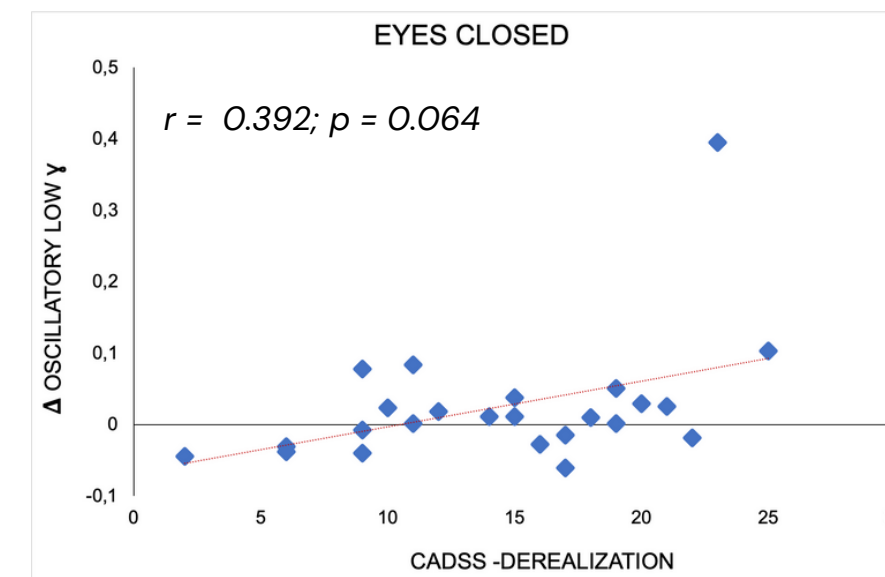
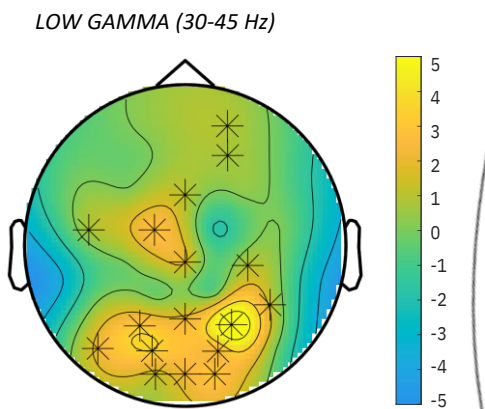
# OSCILLATORY COMPONENT CHANGES

Correlation between **LOW GAMMA OSCILLATORY (30-45 Hz)** component and **CADSS - DEREALIZATION SUBSCALE**

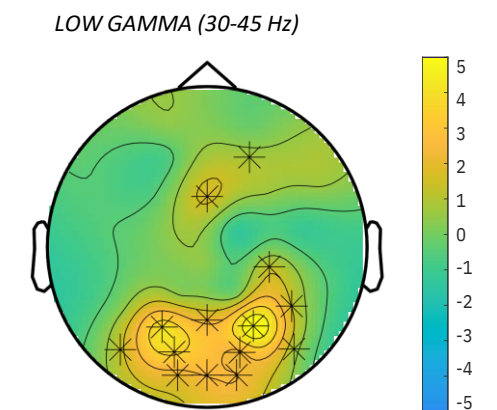
RESULTS



**EYES-OPEN**



**EYES-CLOSED**

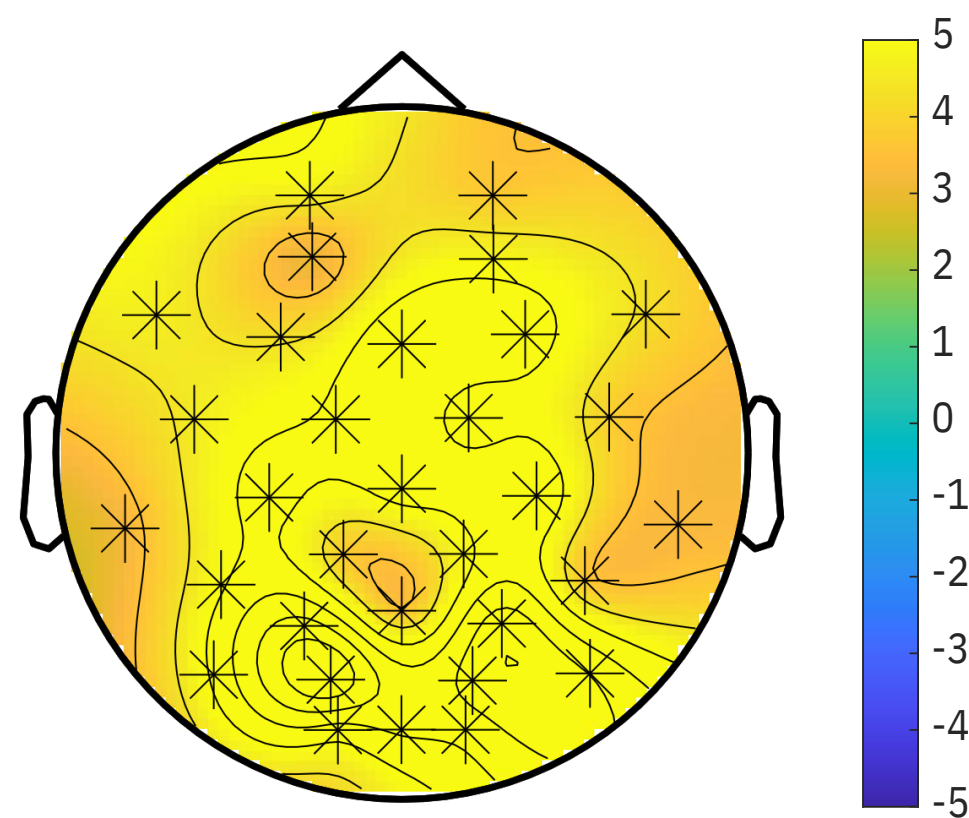


# EEG COMPLEXITY CHANGES

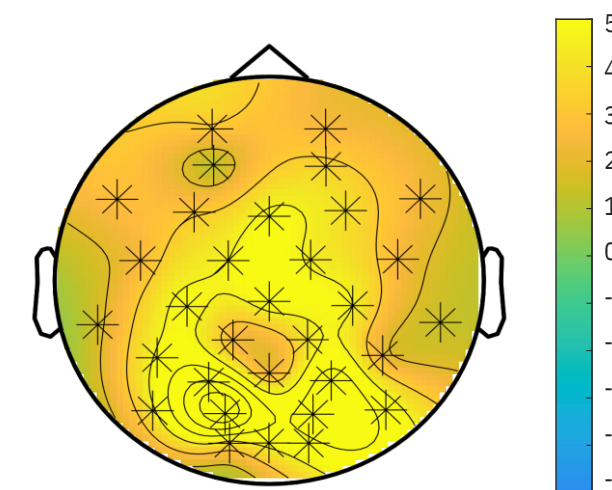
POST vs PRE Lempel-Ziv '76 complexity estimator:

- INCREASE in Entropy after ketamine infusion

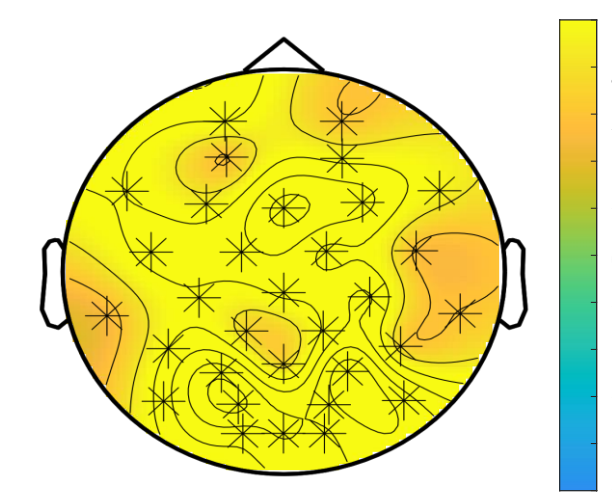
## ENTROPY



## EYES-OPEN



## EYES-CLOSED





## WHAT WE FOUND OUT SO FAR

IV Ketamine seems to determine:

- 🌀 Decrease of power in Delta, Theta, Alpha, and Beta bands
- 🌀 Increase in oscillatory Low Gamma power
- 🌀 Increase neural complexity in TRD (First evidence)

These results are shown in both EO and EC conditions

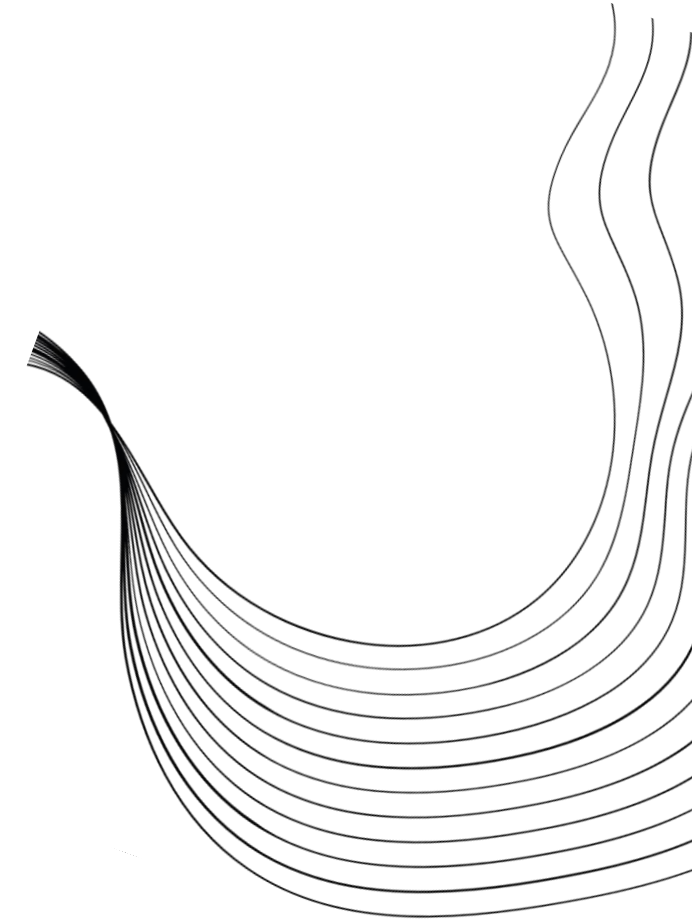
In addition, Low Gamma oscillatory component seems to correlate with higher score in Derealization

## STUDY LIMITATIONS:

- ⌘ Not complete sample, study is still ongoing
- ⌘ Limited spatial resolution due to the 32-channel EEG cup
- ⌘ Different ketamine dosage

## FUTURE DIRECTIONS:

- ⌘ Analysis of the EEG signal during IV ketamine infusion;
- ⌘ Evaluate the role of ketamine-induced derealization in depressive symptomatology (including MADRS results in the analysis);
- ⌘ Evaluate if more EEG entropy could be a marker of richer phenomenological experience which could lead to a better insight and ameliorate depressive symptoms





# Acknowledgement



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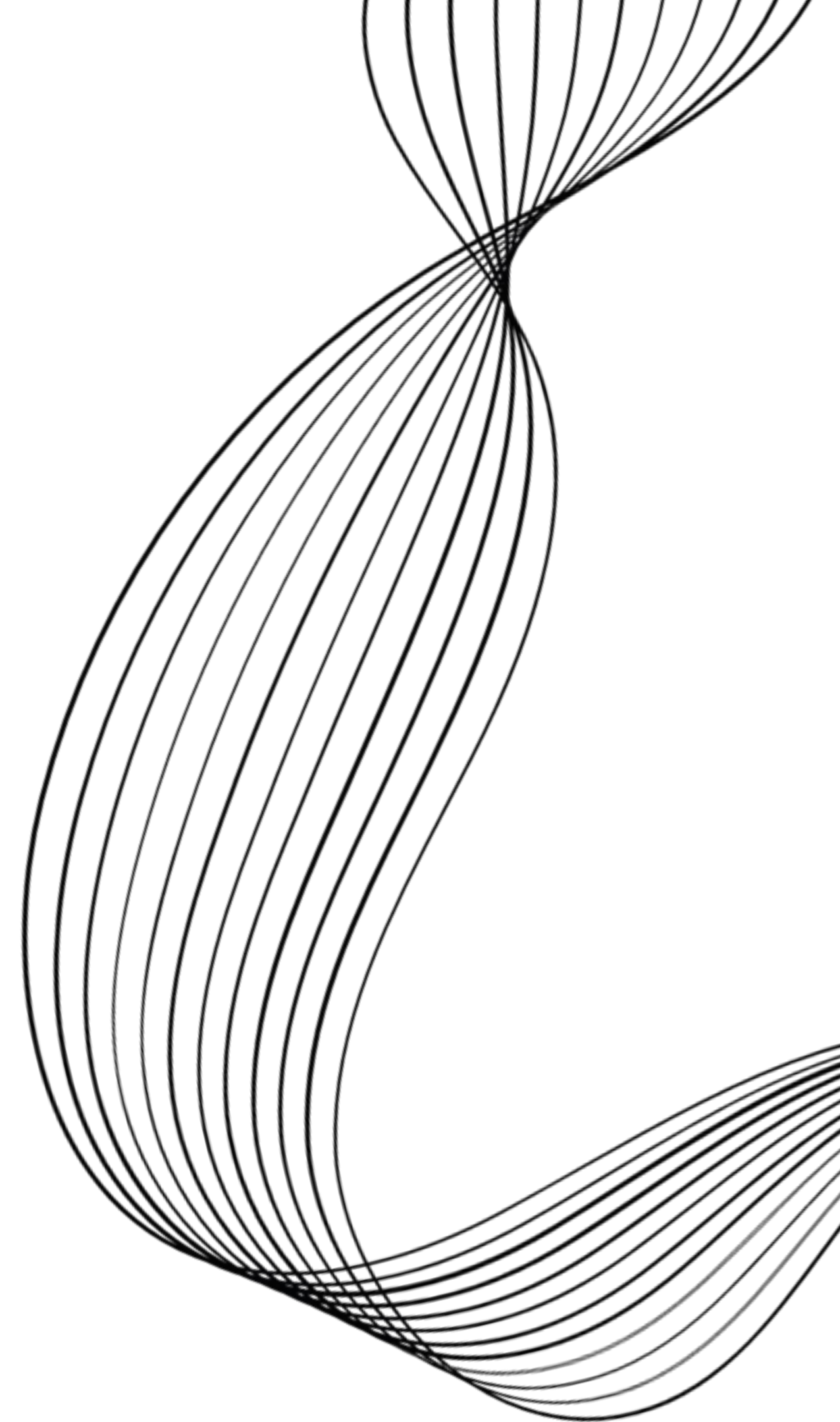
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**THANK YOU  
FOR YOUR  
ATTENTION**

