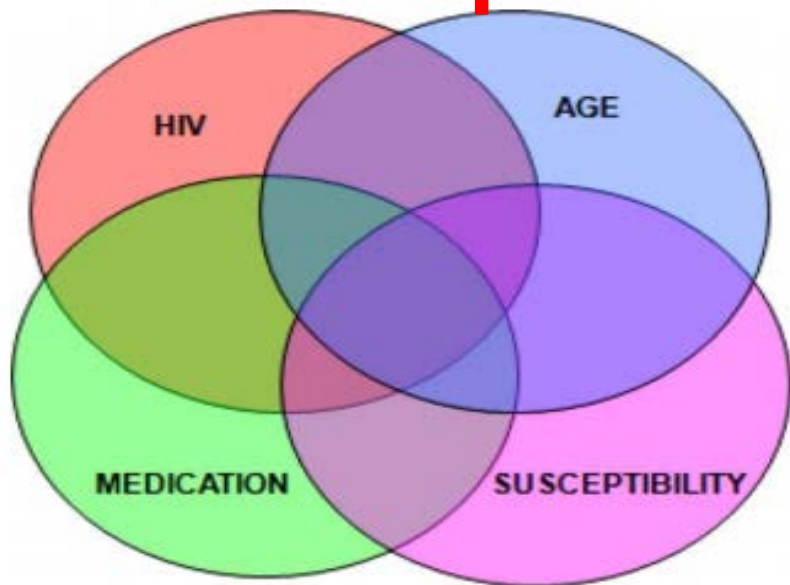


RESTING STATE CONDITION EEG-LORETA AND CSF BIOMARKERS IN PATIENTS WITH HAND

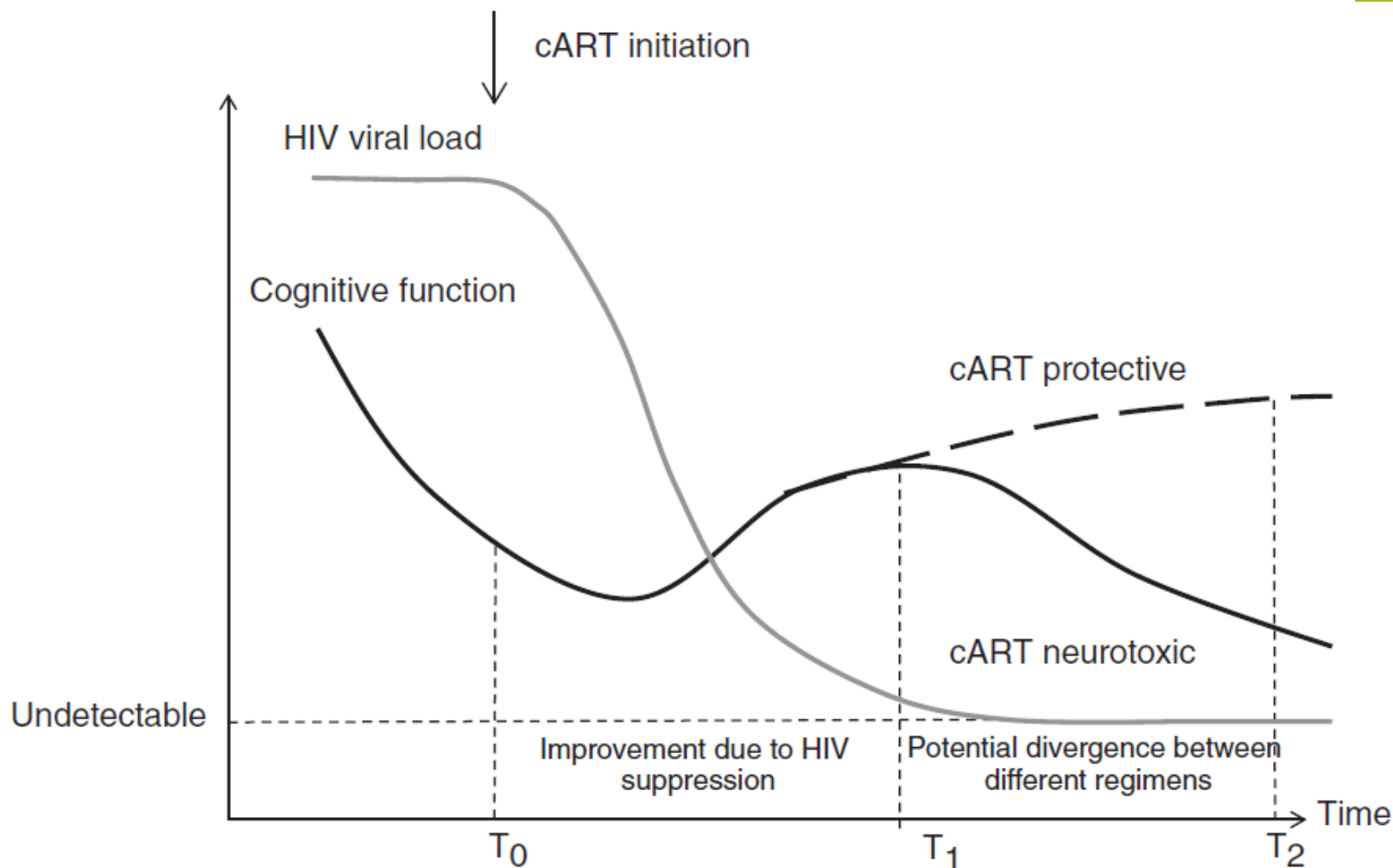
Alessandro Lazzaro – 14-15/06/2019

Factors implicated in HAND neuropathogenesis



- Viral escape
- Priming of microglia
- Blood brain barrier impairment
- Amyloid beta $A\beta_{42}$?
- HIV proteins Vpr, Tat, Nef gp120
- Metabolic syndrome

ART related neurotoxicity model.



HIV ASSOCIATED NEUROCOGNITIVE DISORDER

- HIV induced **neuropathological changes** : 80–90 % of subjects without HAART
- **subclinical neuropathy** : 10–40 % of asymptomatic HIV and AIDS subjects
- **neurological symptoms** : 50–100 % of subjects during the course of illness
- **Is prevalence** of neurological and neuropsychological symptoms **increasing?**

QUEST FOR BIOMARKERS

indexing the HIV effects on brain function

- for clinical purposes,
- for drug discovery and monitoring

NEUROPSYCHOLOGICAL
TEST

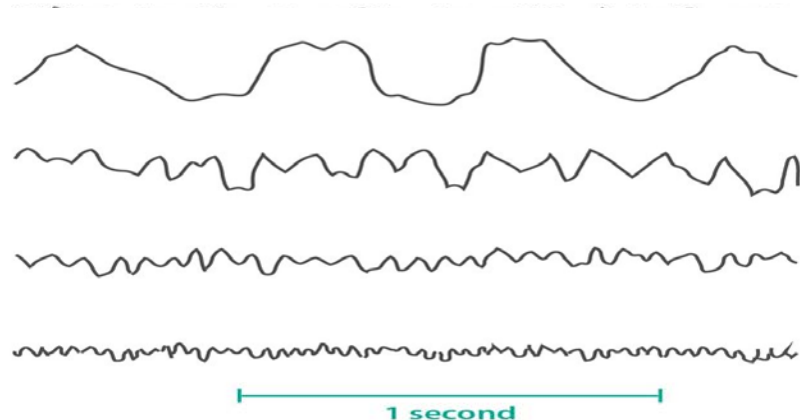
EEG

CSF
BIOMARKERS

eyes-closed resting state condition ELECTROENCEPHALOGRAPHAM rs-EEG

recording of **electroencephalographic rhythms** at electrodes placed on the scalp while subjects with HIV stay **in quiet wakefulness**

- measurement of brain function
- *cost-effective*
- *non-invasive*



Band	Frequency (Hz)
Delta	< 4
Theta	≥ 4 and < 8
Alpha	≥ 8 and < 14
Beta	≥ 14

In PLWH

- **decrease of alpha** (8–12 Hz) rhythms when compared to healthy
- **Increase of delta** (2–4 Hz) **and theta** (4–7 Hz) rhythms which are abnormally high in amplitude, similarly to a classical observation reported in seniors with cognitive symptoms
- **In 20–30%** of HIV subjects, there is a paradoxical and poorly understood **increase in the alpha rhythms** which might be related to the evolution of the infection or some mental symptoms

LORETA

**Low Resolution Electromagnetic Tomography
Standardized & Exact & Zero-error forever**

Functional Connectivity

[LORETA-KEY[®]]

Functional localization

FUNCTIONAL IMAGING TECHNIQUE : **LINEAR INVERSE SOLUTION PROCEDURE**

MODELING THE 3D DISTRIBUTIONS OF EEG

NO A PRIORI DECISION OF DIPOLE POSITION REQUIRED

THE 3D DISTRIBUTIONS OF EEG MODEL : **3-SHELL SPHERICAL HEAD MODEL**

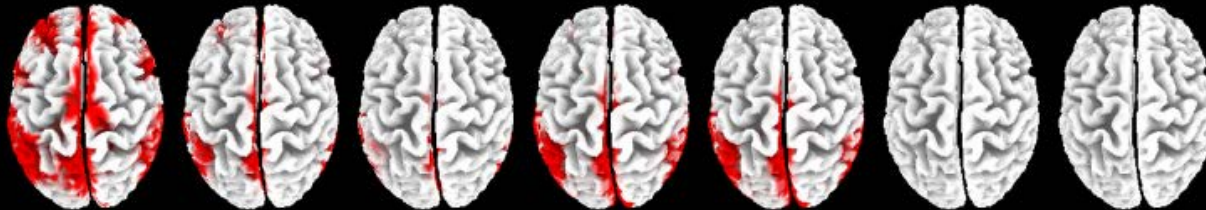
SCALP - SKULL - BRAIN (CORTICAL GRAY MATTER/HIPPOCAMPUS)

2394 VOXELS - SPATIAL RESOLUTION : **7mm**

GRAND AVERAGE OF LORETA CURRENT DENSITY

Delta Theta Alpha1 Alpha2 Alpha3 Beta1 Beta2

HIV

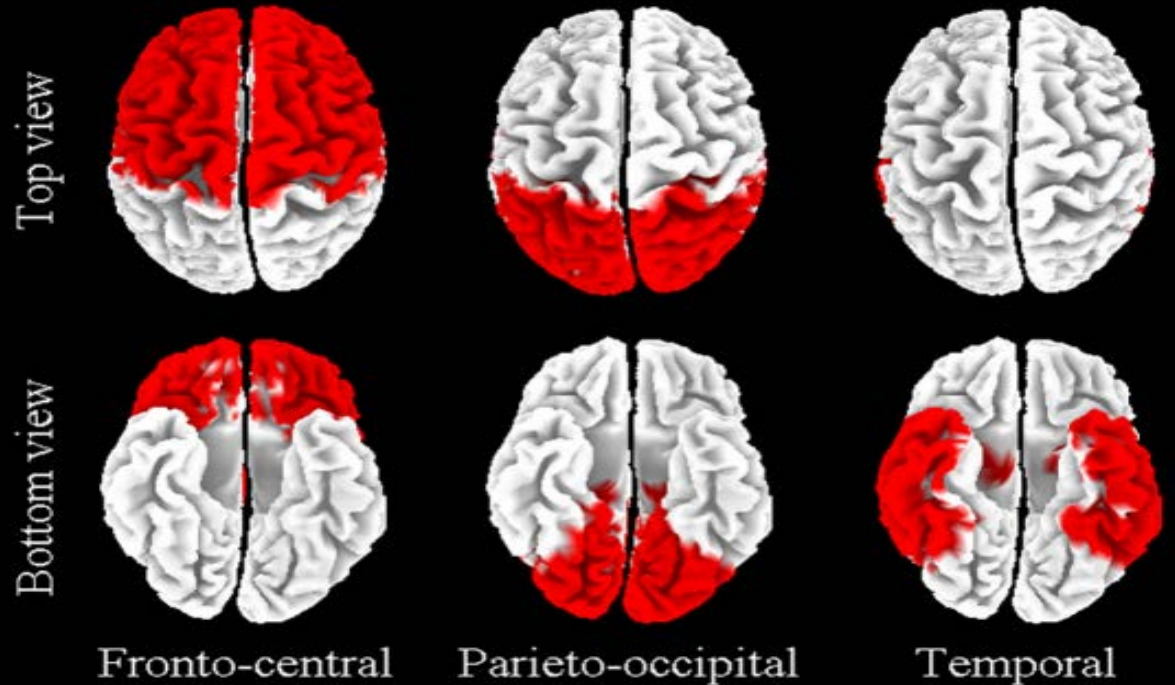


Healthy



0 max

REGIONS OF INTEREST (ROIs)



Brodmann

areas

1 - 2 - 3 - 4 - 6

8 - 9 - 10 - 11

44 - 45 - 46 - 47

5 - 7 - 17

18 - 19 - 30

39 - 40 - 43

20 - 21 - 22

37 - 38 - 41 - 42

MARAND X

SINGLE-CENTRE, OPEN-LABEL, RANDOMISED PILOT STUDY OF 180 DAYS DURATION

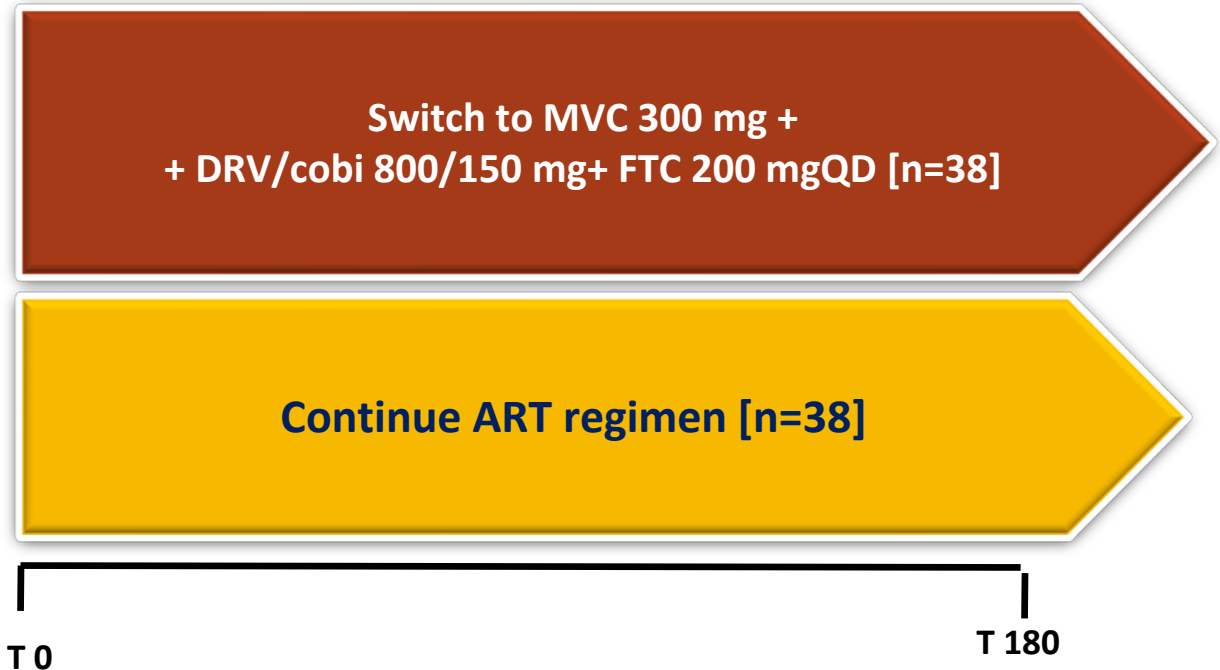
INCLUSION CRITERIA

- HIV+
- HAND diagnosed
- on suppressive ART
- plasma VL ≤ 50 c/mL
- CSF VL ≤ 50 c/mL
- R5 tropic virus
- No major resistance on plasma nor CSF

EXCLUSION CRITERIA

- Efavirenz e/o Darunavir containing ART
- R4 or Dual tropic virus
- Major resistance on plasma nor CSF
- Drug-drug interactions
- Comorbidities influencing SNC performance: CNS pathologies, Head Injury history, Mental retardation, Anxious Depressive Syndrome, Cirrosys, CKD, Alcoholism, ongoing infective, autoimmune and/or neoplastic disease

Randomization
1:1



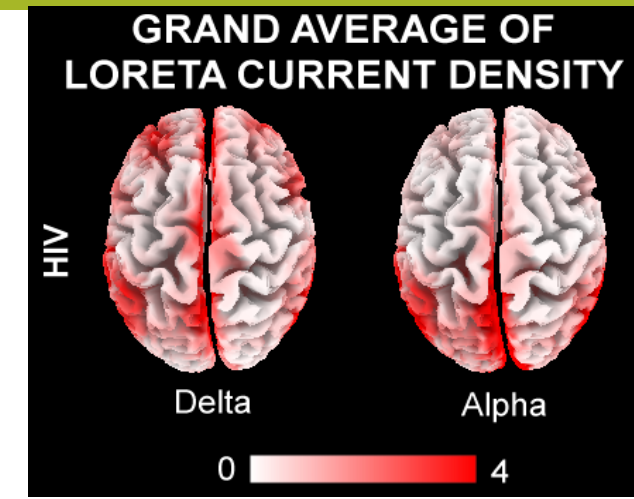
T 0
NPS
rs-fMRI
rs-EEG
LP
Fibroscan
IMT

T 180
NPS
rs-fMRI
rs-EEG
LP
Fibroscan
IMT

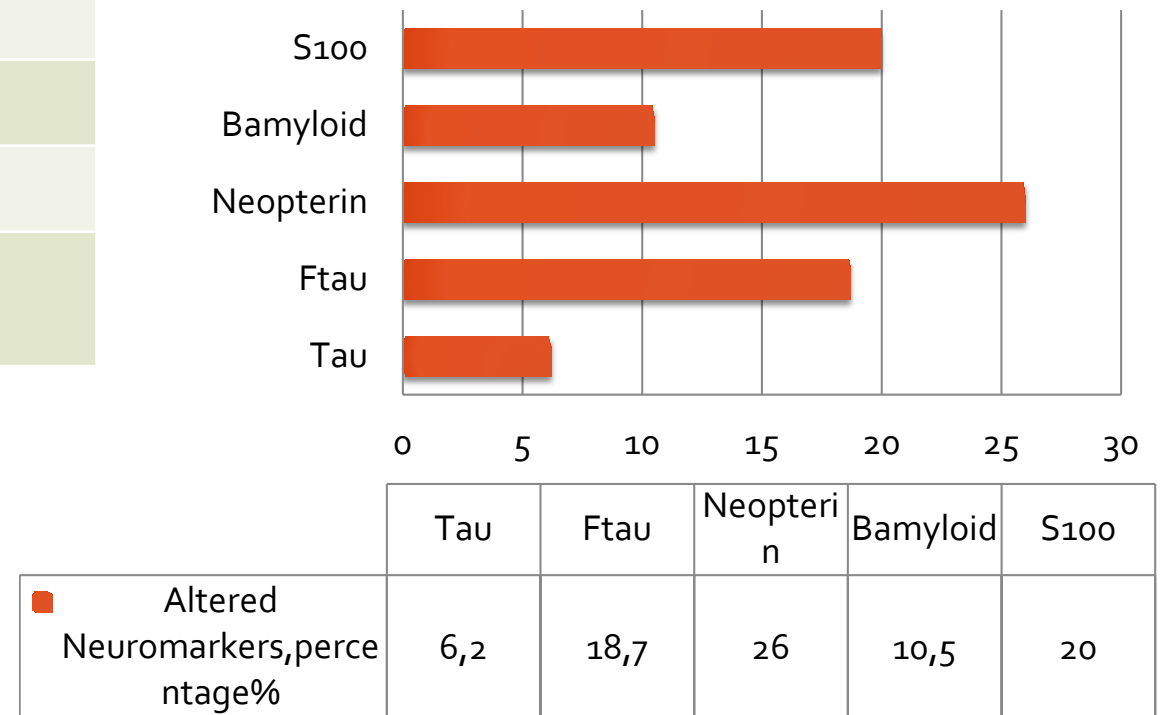
A NOVEL COHORT OF "CLEAN PATIENTS" WITH HAND

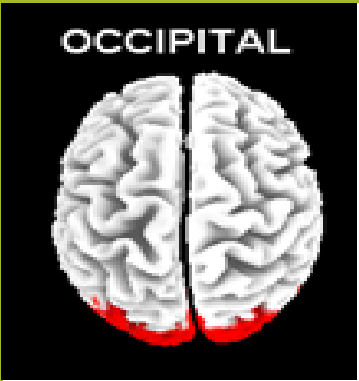
PATIENTS ENROLLED	Absolute value (% or IQR)
Total	32
Male gender	22 (70%)
Age – years	57 (49-63)
BMI - Kg/m ²	24,2 (23,5-25,0)
Current CD4 ⁺ - cells/ μ L	600 (427-745)
Nadir CD4 ⁺ - cells/ μ L	369 (153-443)
Virological Suppression – years	11 (5-13)

HAND	32 - (100%)
ANI	30 - (93,8%)
MND	2 - (6,2%)



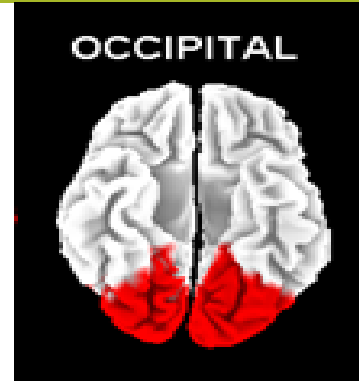
Altered Neuromarkers,percentage%





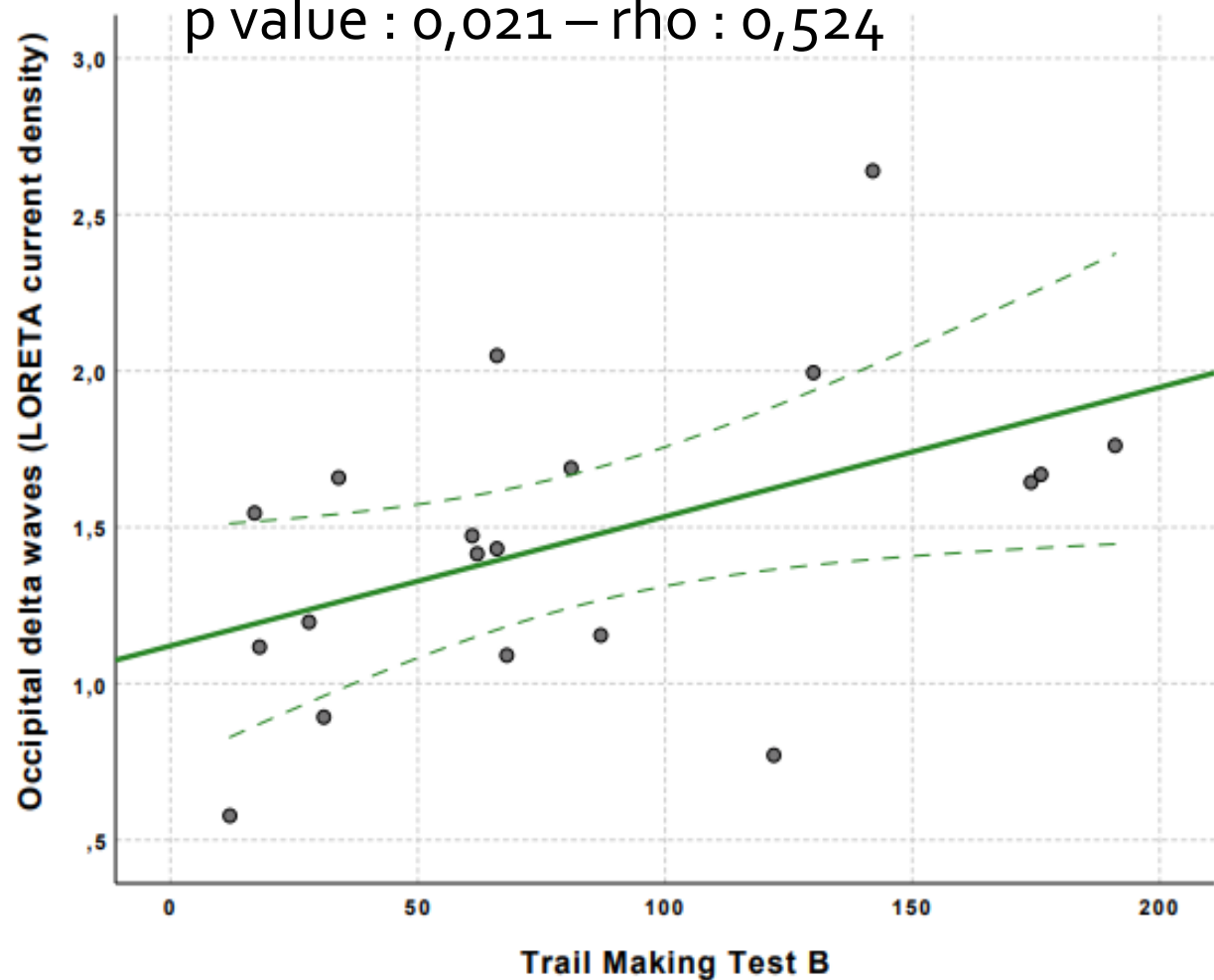
OCCIPITAL

SCATTERPLOT BETWEEN EEG BIOMARKER & NEUROPSYCHOLOGICAL TEST

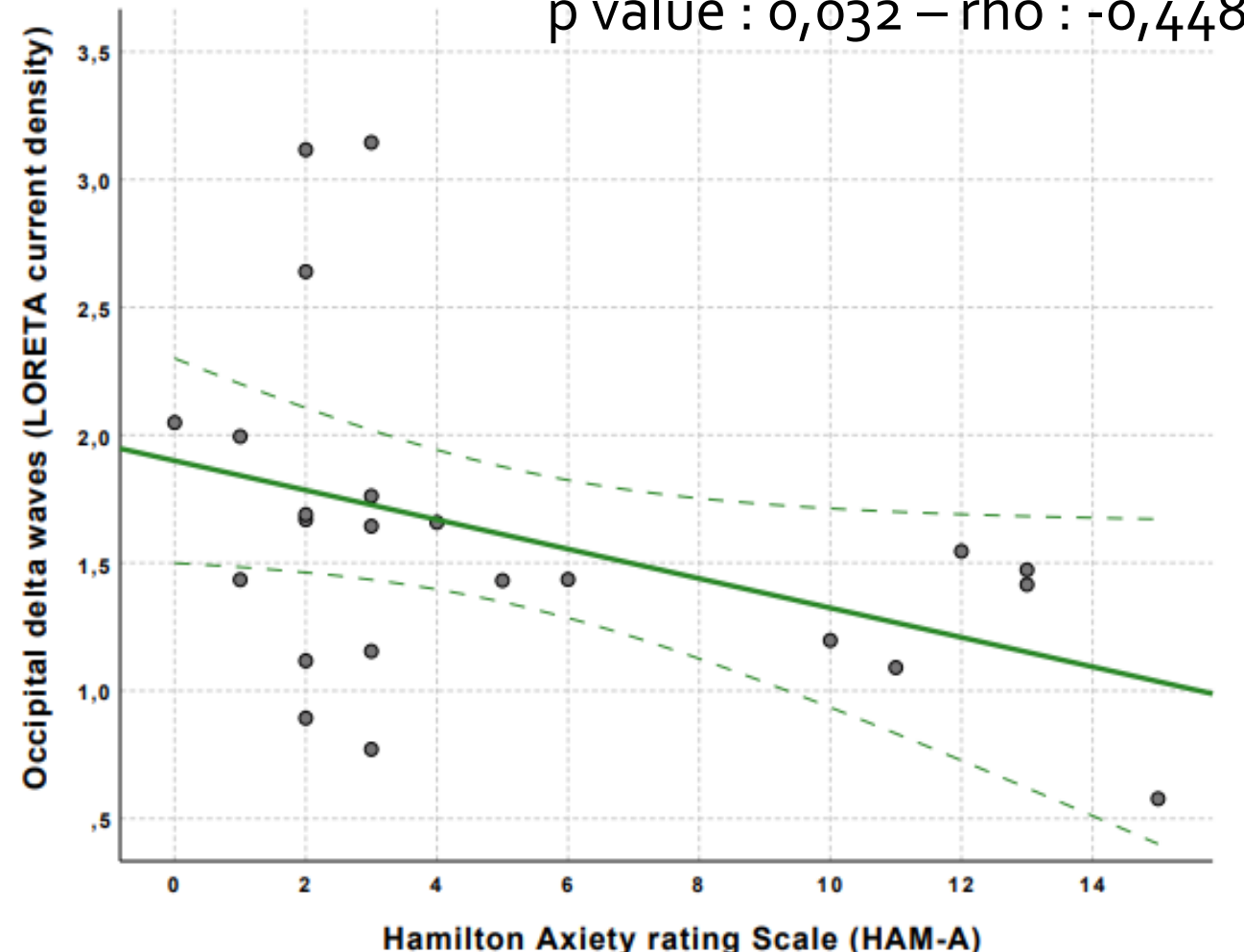


OCCIPITAL

p value : 0,021 – rho : 0,524



p value : 0,032 – rho : -0,448



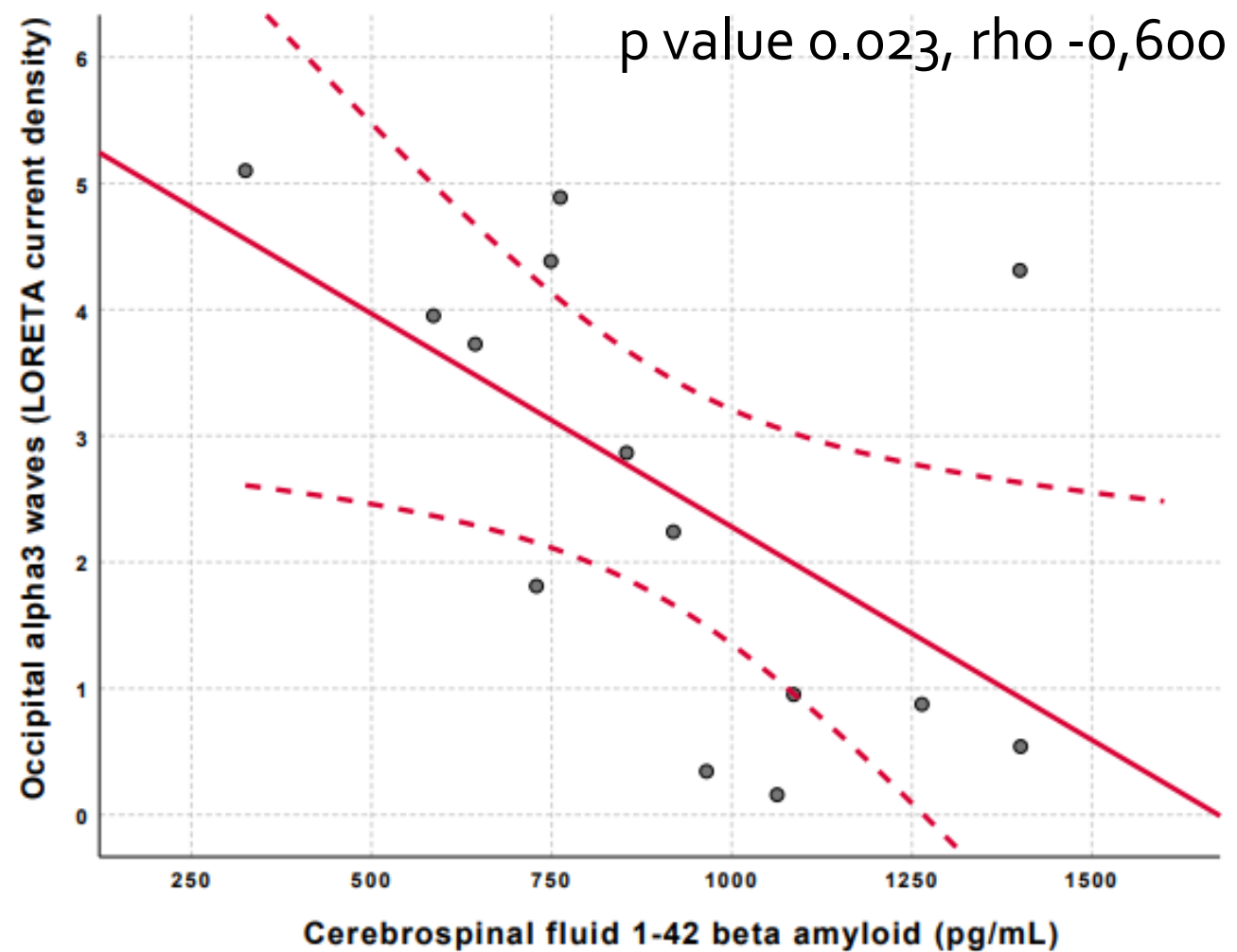
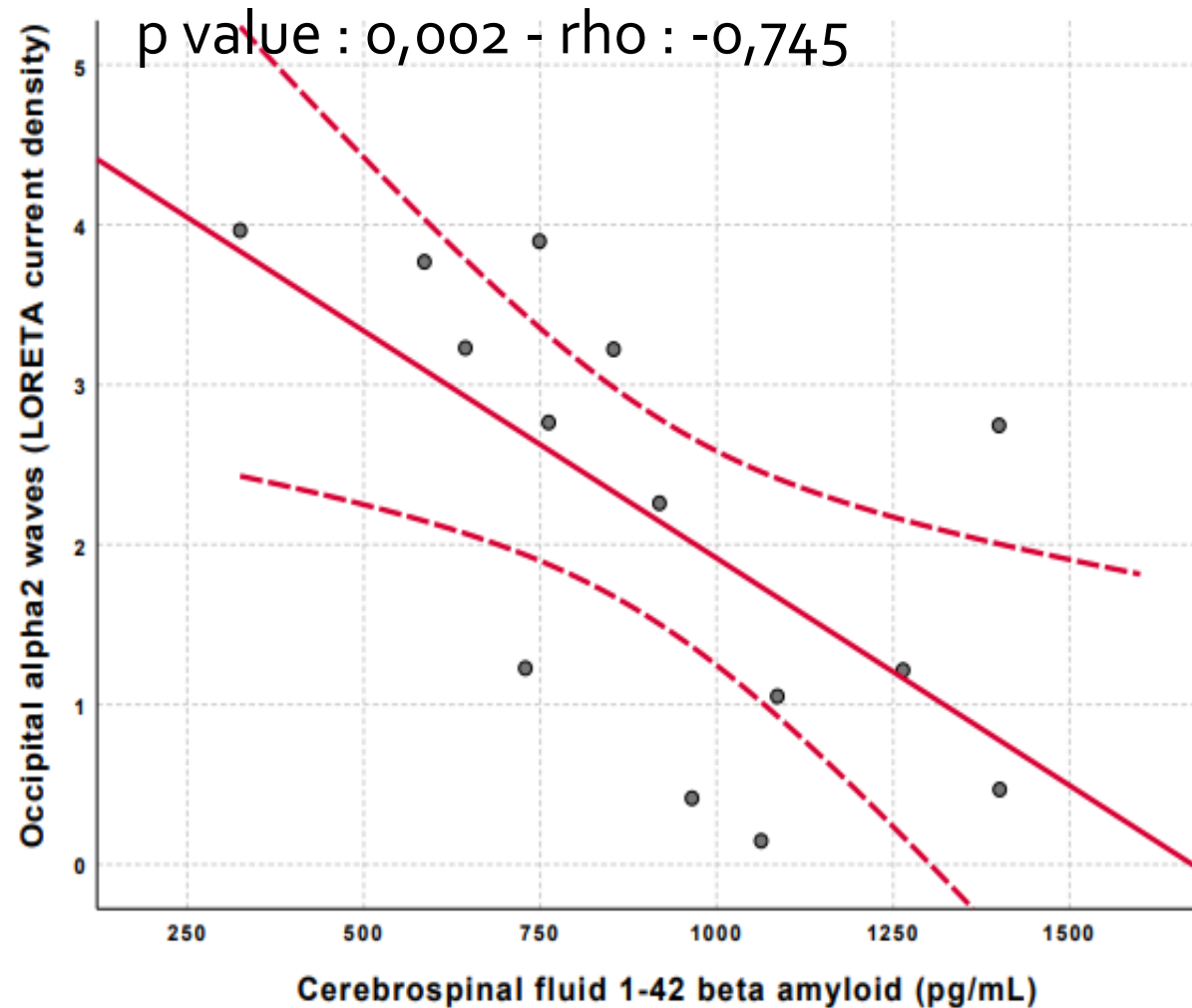
OCCIPITAL

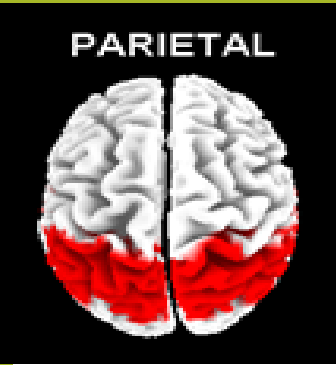


SCATTERPLOT BETWEEN EEG BIOMARKER &

CEREBROSPINAL FLUID BIOMARKERS

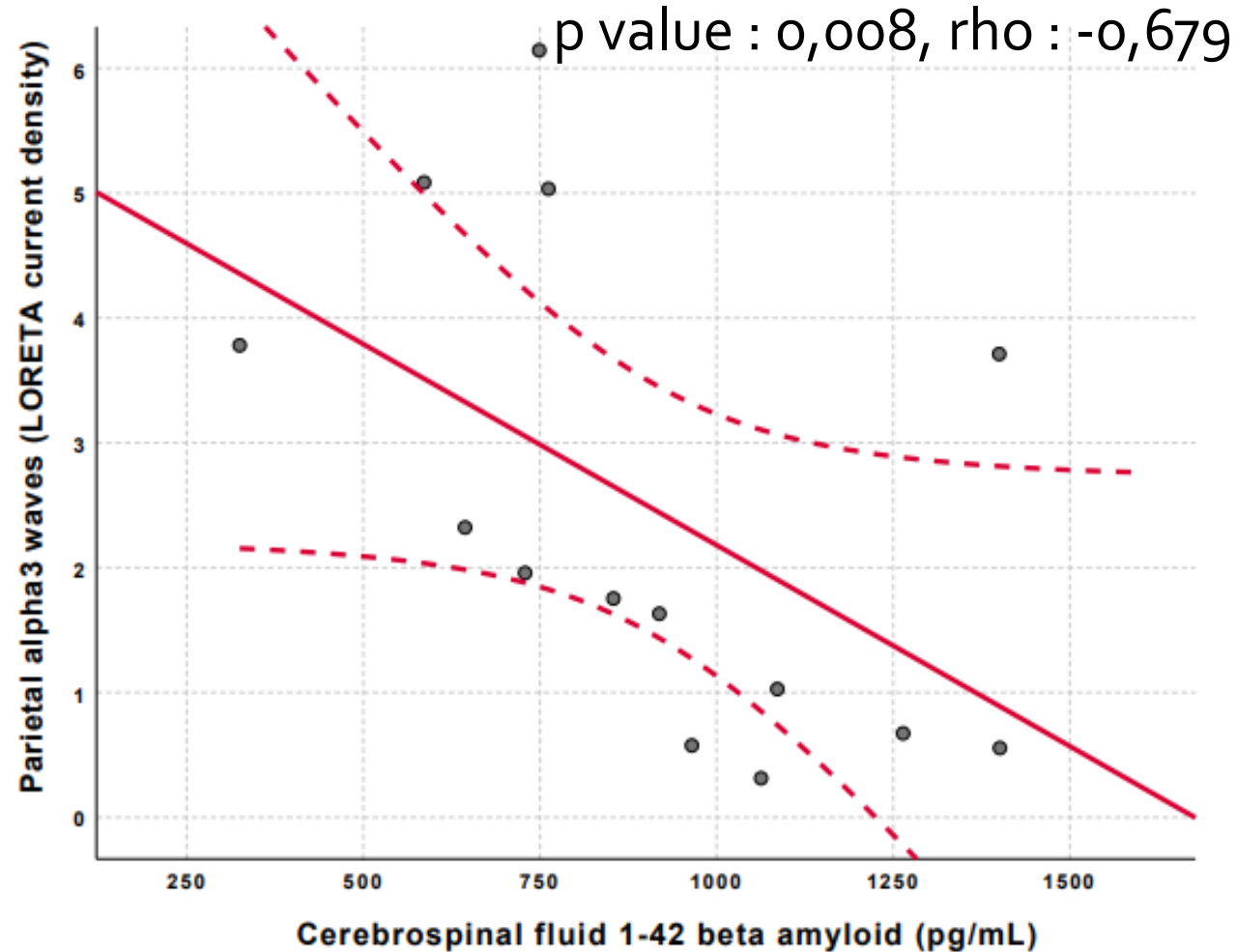
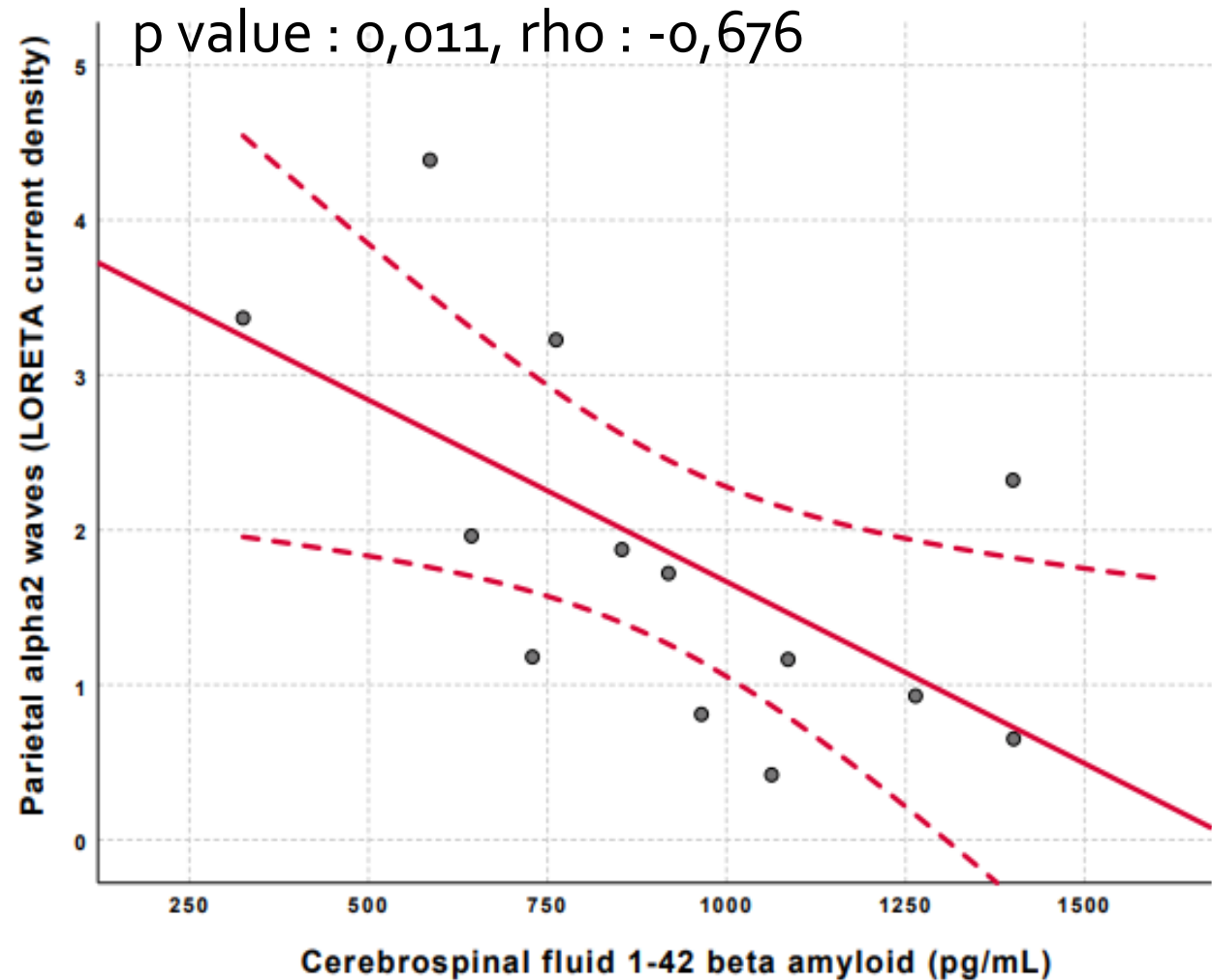
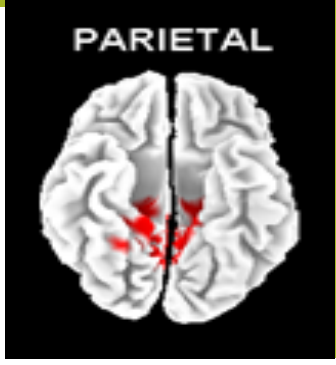
OCCIPITAL





SCATTERPLOT BETWEEN EEG BIOMARKER &

CEREBROSPINAL FLUID BIOMARKERS



STATISTICAL ANALYSIS

NEUROPSYCHOLOGICAL TEST

Occipital delta source activity (<4 Hz) was associated with:

- longer executive functions (**Trail making B**)
- worse score in Hamilton Anxiety Scale (**HAM-A**)

CSF BIOMARKER

Global alpha₂ and alpha₃ source activity (8-12 Hz)

- were **lower**
- and strongly associated with **higher CSF βA_{42}**

CONCLUSIONS

- rsEEG source activity at **delta and alpha rhythms may reflect brain dysfunction** in HIV patients with HAND and were specifically related to **altered executive functions**, often altered in cognitively impaired individuals
- The association of **alpha** source activity in patients with **CSF β -amyloid** protein warrant further studies to assess neurotoxicity and ageing among PLWH.
Possible role of ART on **β Amyloid₄₂ metabolism**
- These are the baseline data of an ongoing study. More data from this cohort could lead to important features for using rsEEG in the assessment of potential neurotoxicity and in the long-term follow up of ageing PLWH