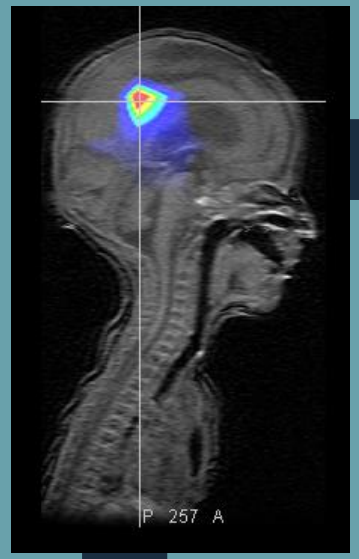
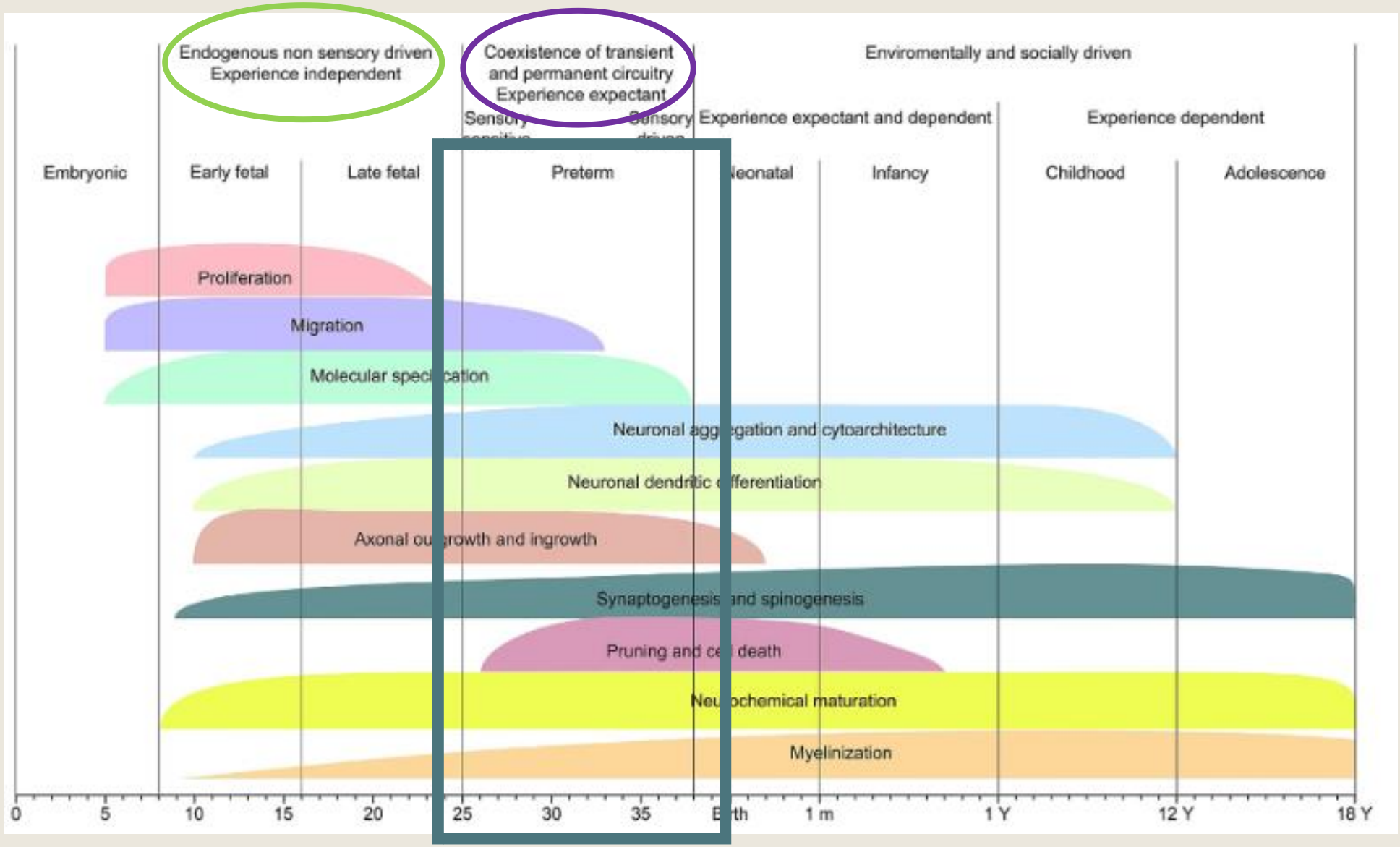


To the topic *BRAIN FUNCTIONAL MATURATION* we answer *EEG-HR!* Why ?

Dr Laura Routier
Praticien Hospitalier Universitaire, GRAMFC INSERM U1105
Neobrain 2 - 14/06/2021



Kostovic et al. 2019

A transient brain organization

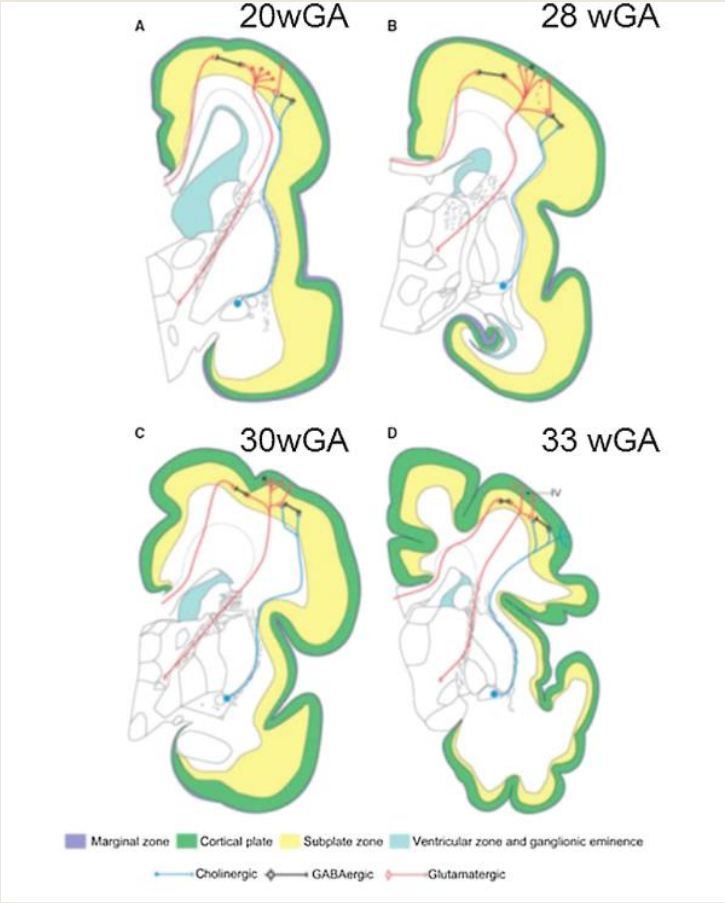
- Dual innervation with the cortical plate and subplate

- Before 26 wGA
  - Very immature cortical plate
  - A well-developed subplate
  - Synapses between the neurones of the subplate and the quiescent thalamic afferents

- 28 wGA : a crucial moment in brain maturation
  ➔ relocation of thalamic afferents into the immature cortical plate

- Involution of the subplate from 28 wGA

At the 3rd trimester of gestation, transition between
➔ Very early endogenous genetically encoded activities
➔ And modulation of cortical activities by sensory experience



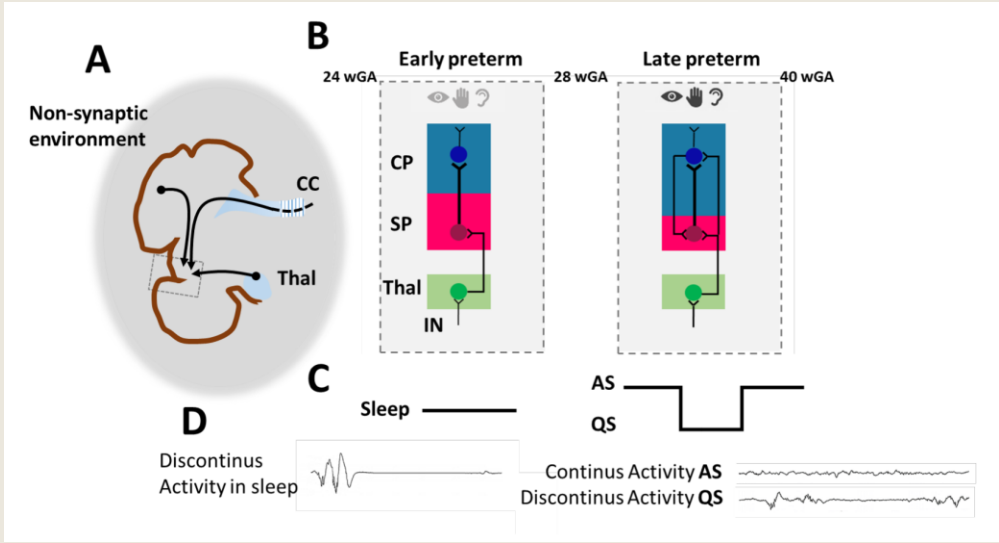
Kostović et al. 2010

The subplate: a key structure

- Involvement in the development and plasticity of the cortical plate
- Establishment and functional maturation of thalamo-cortical connections
- Feedback projections to the thalamus
- The activity-dependent development of cortical columns
- Radial neural migration

- In vitro, active role of the subplate in the genesis of spontaneous cortical activities in the auditory system

Zhao et al., 2009

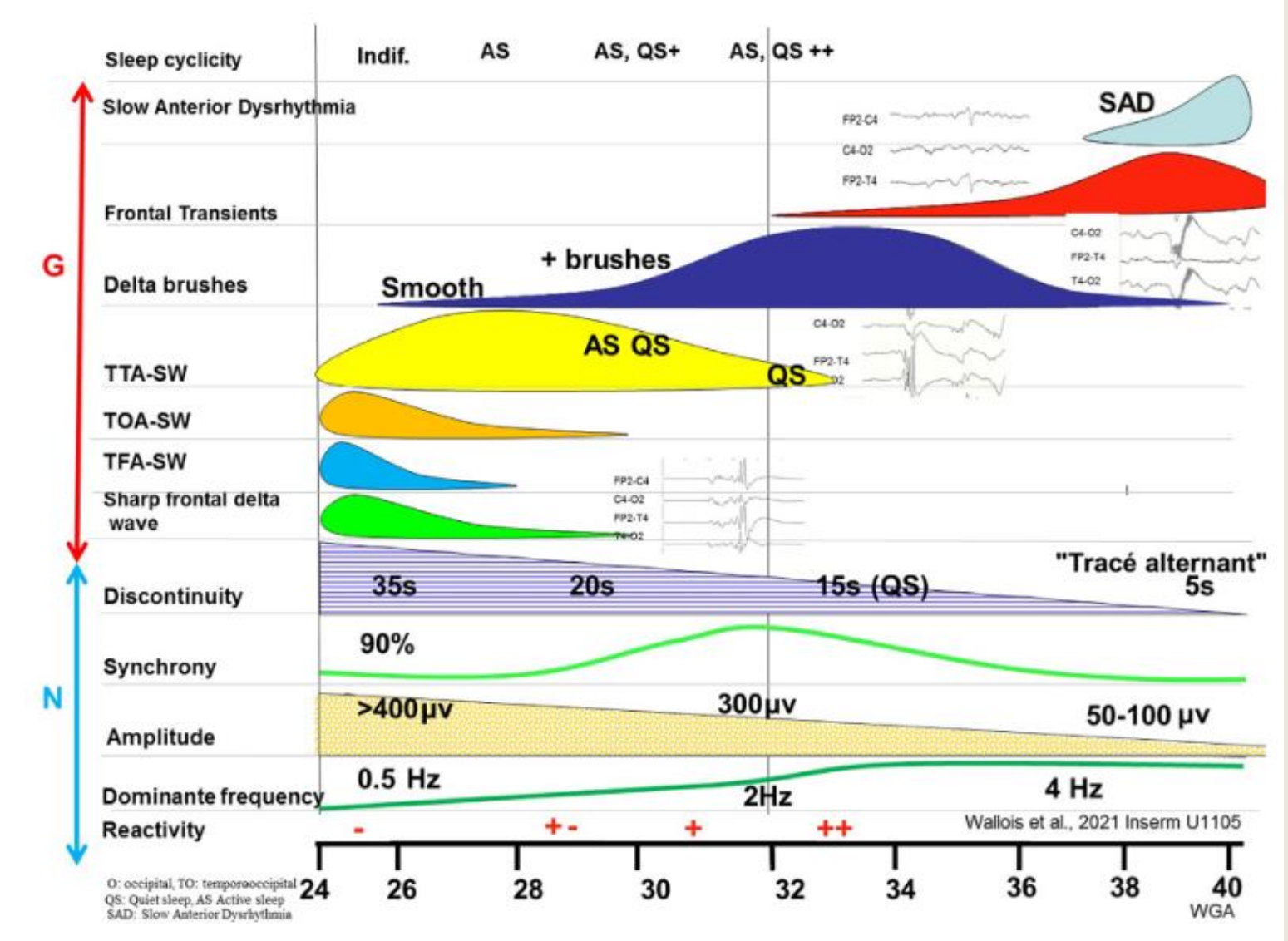


Wallois et al. 2021

EEG of the premature newborn

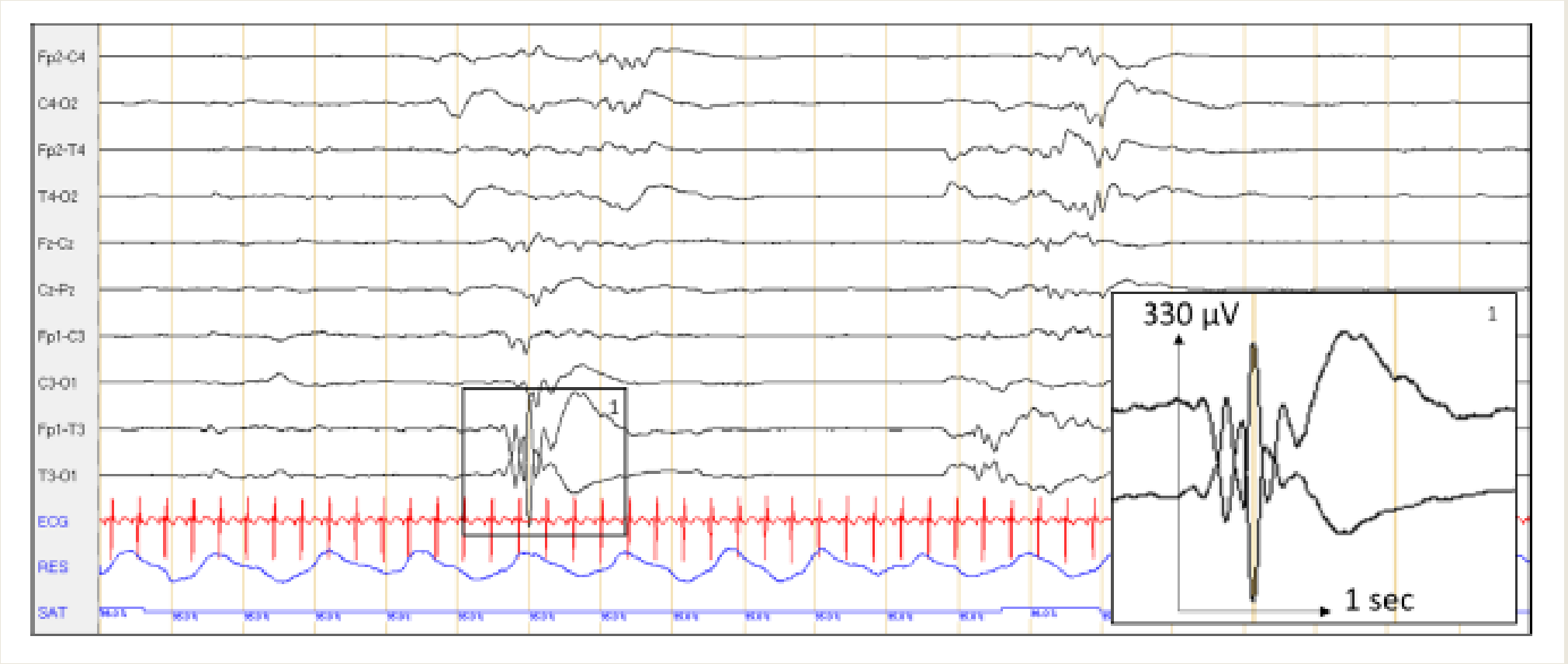
Generator based dynamic

Network based dynamic



Wallois et al. 2021

Eeg discont


Fp2-C4
C4-O2
Fp2-T4
T4-O2
Fz-Cz
Cz-Pz
Fp1-C3
C3-O1
Fp1-T3
T3-O1
ECG
RES
SAT
1
330 µV
1
1 sec

Unanswered questions…

- Role of these physiological neurobiomarkers?
- Genetically encoded? Modulated by sensory experience?
- Location of the generators/oscillators of these biomarkers?
- Role of these activities in the functional maturation?
- How pathological processes occurring in- or ex-utero can impact these activities and long-term consequences for the neurodevelopmental outcome?

➔ Study in EEGHR! !

Hum Brain Mapp. 2017 May;38(5):2345-2358. doi: 10.1002/hbm.23521. Epub 2017 Jan 23.

Plasticity of neonatal neuronal networks in very premature infants: Source localization of temporal theta activity, the first endogenous neural biomarker, in temporoparietal areas

L Routier [1,2], M Mahmoudzadeh [1], M Panzani [1], H Azizollahi [1], S Goudjil [1,3], G Kongolo [1,3], F Wallois [1,2]

Affiliations + expand

PMID: 28112458 PMCID: PMC6867100 DOI: 10.1002/hbm.23521

Free PMC article

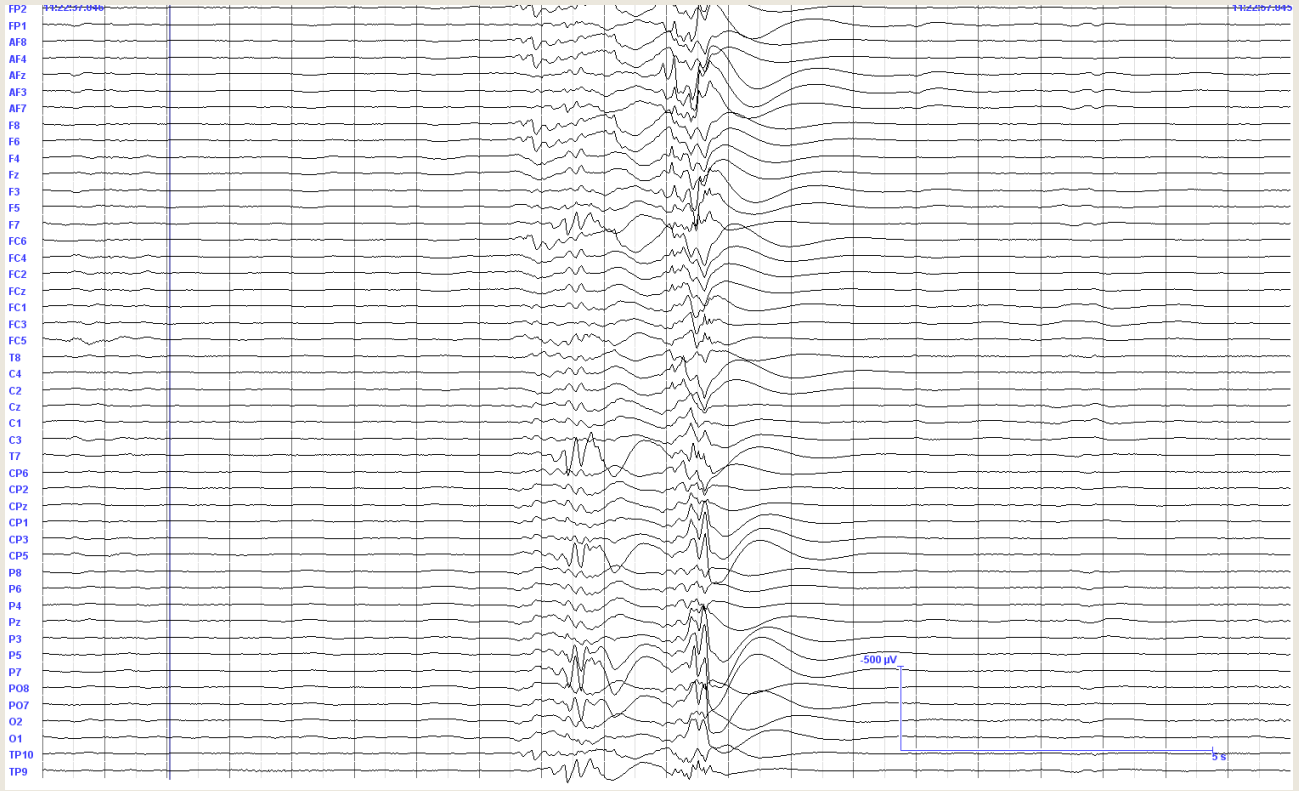
TTA-SW = Temporal theta activities in coalescence with a slow wave

TTA-SW

- 24-32 wGA (max 28-30 wGA)
- Bursts of high amplitude (20-300 µV) theta activities (4-7,5 Hz)
- In coalescence with a positive SW
- Seen during active periods
- Favorable neurological prognosis
- Generator, functionality and location remain unknown

➔ TTA-SW: Acquired or innate early biomarker?

EEG standard HR à 26 sAC – montages bipolaire et référentiel – amplitude 15 uv/mm pages de 20 s – bande passante 0,5-40 Hz

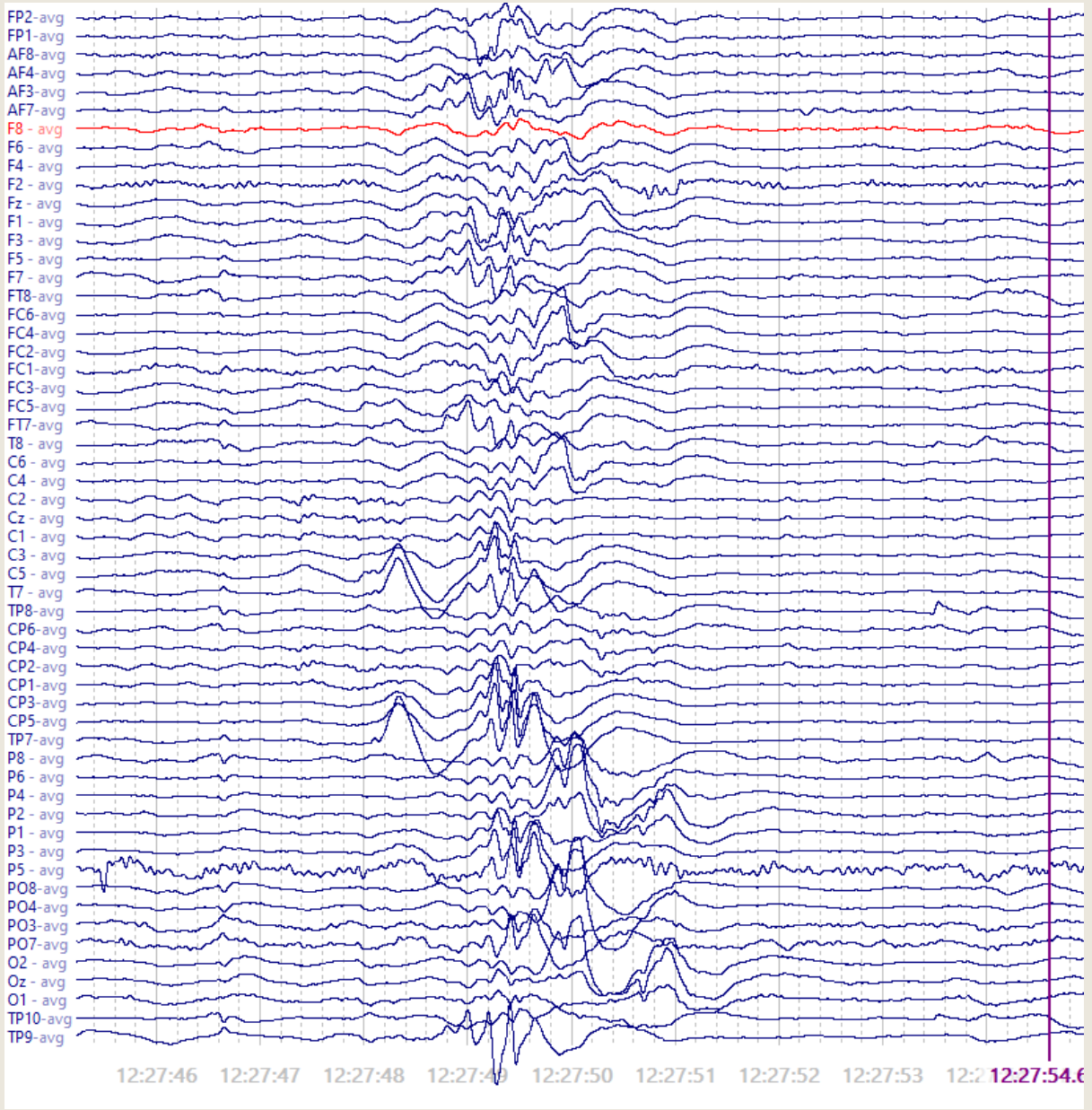


➔ HD-EEG of 14 healthy premature newborns recorded at 26-31 sAC


AF8-Ave
AF4-Ave
F8-Ave
F6-Ave
F4-Ave
F2-Ave
FT8-Ave
FC6-Ave
FC4-Ave
FC2-Ave
T8-Ave
C6-Ave
C4-Ave
C2-Ave
TP8-Ave
CP6-Ave
CP4-Ave
CP2-Ave
P8-Ave
P6-Ave
P4-Ave
P2-Ave
PO8-Ave
PO4-Ave
O2-Ave
AFz-Ave
Fz-Ave
FCz-Ave
Cz-Ave
CPz-Ave
Pz-Ave
POz-Ave
Oz-Ave
AF7-Ave
AF3-Ave
F7-Ave
F5-Ave
F3-Ave
F1-Ave
FT7-Ave
FC5-Ave
FC3-Ave
T7-Ave
C3-Ave
C5-Ave
C1-Ave
TP7-Ave
CP3-Ave
CP5-Ave
CP1-Ave
P7-Ave
P5-Ave
P3-Ave
P1-Ave
PO7-Ave
PO3-Ave
O1-Ave

Descriptive analysis

- Very focal activities under 2 to 7 electrodes
- On the temporal (T7, T8) and centro-parietal (CP5, CP6) electrodes
- More diffuse at 26 than at 31 wGA but located in the same regions
- Same characteristics of the slow waves

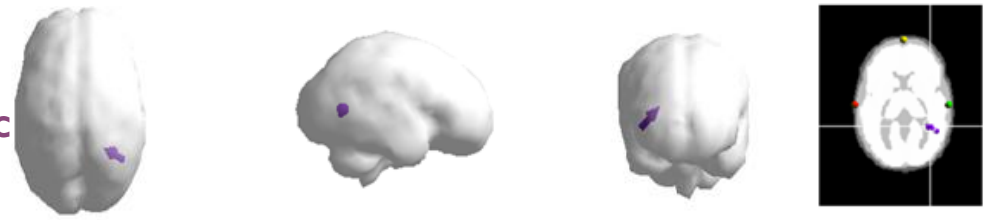


Source location on grand averaging

- Location in the posterior superior temporal sulcus
- No superficial but deep location
- Deeper at 26-29 wGA (14.7 vs 9.5 mm)

- Similar location of the slow wave

26-29sAC

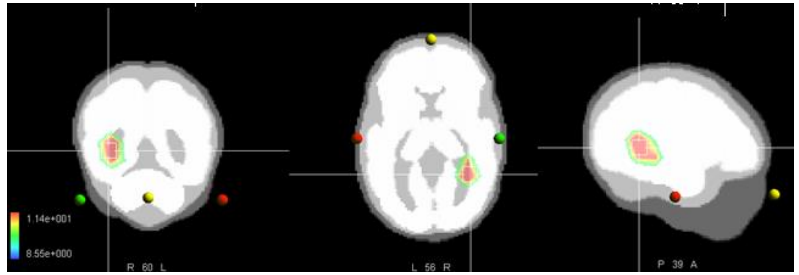


Dipôles moyens des activités thêta droites

30-31sAC

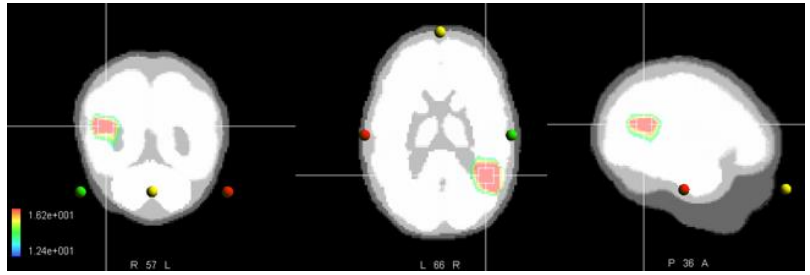
Dipôles moyens des activités thêta droites

26-29 sAC



Localisation MUSIC des activités thêta droites

30-31sAC



Localisation MUSIC des activités thêta droites

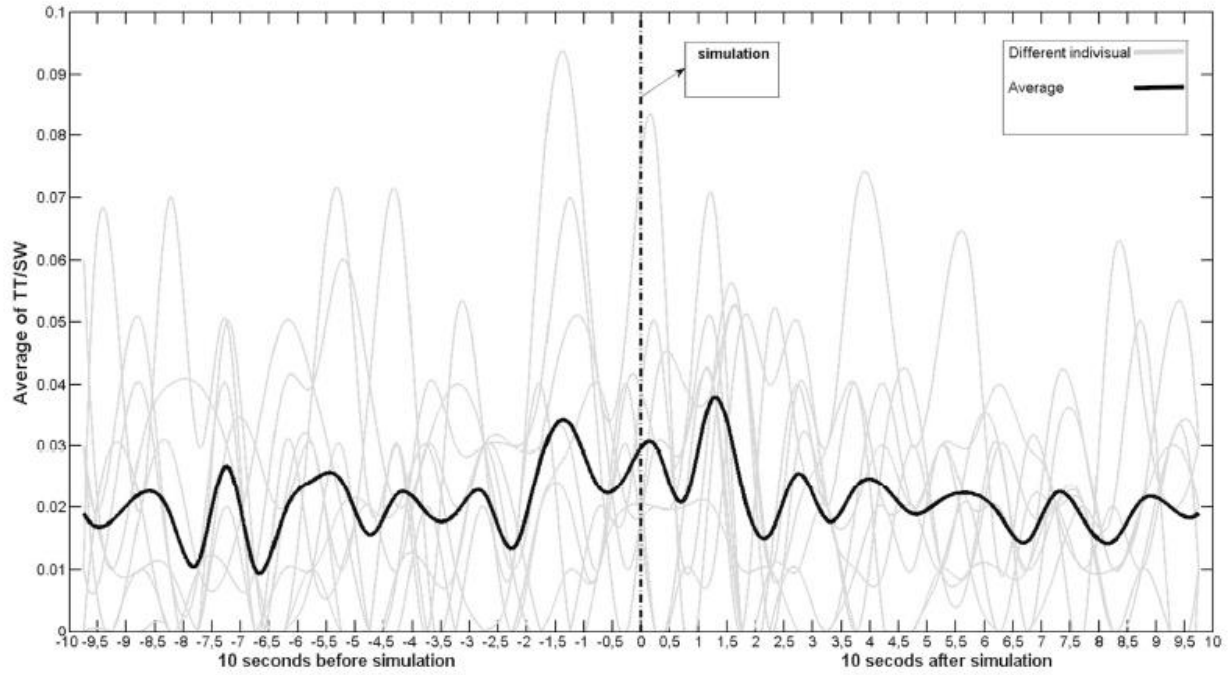
Routier et al. 2017

TTA-SW: Activity dependent on sensorial experience?

- 30 EEG of premature infants between 26-31 wGA
- Auditory clicks
- No modulation or induction of TTA SW by auditory stimuli

➔ An endogenous genetically determined activity

Routier et al. 2017



Effect of click stimuli on the occurrence of TTA-SW. Interpolation of the frequency of TTA-SW occurrence within 0.5 s intervals for each subject and the grand average across subjects

Discussion

- Functional TTA-SW generators from 24 wGA
  - *Before the thalamic afferents reach the immature cortical plate*
  - *Before the sensory experience*

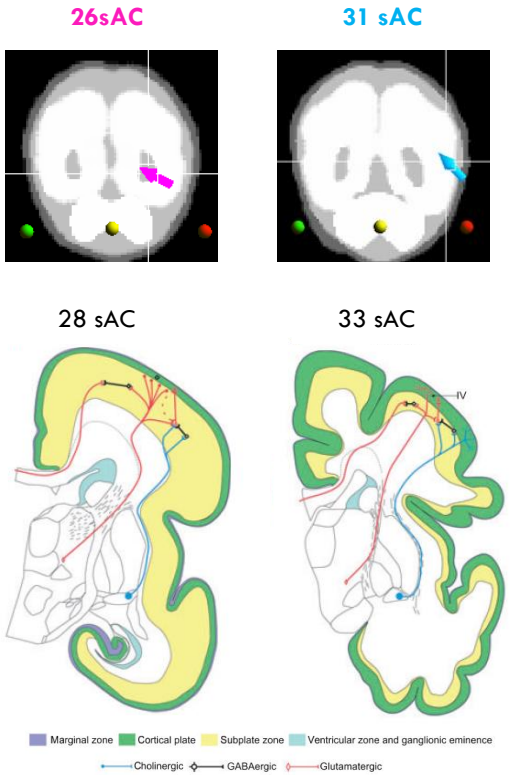
➔ ***The early developmental biomarker of the temporal region***

Origin of TTA-SW?

- In the subplate?
  - *Significant and early synaptic activities*
  - *Receives thalamic afferents*
  - *Endogenous spontaneous activity (bursts of discontinuous activity) from 20-21 wAG in vitro in the absence of sensory experience*

    Moore et al. 2011
  - *Migration of TTA-SW correlated with the involution of the subplate*

- Where does the activity recorded on the surface come from?
  - *Closed fields linked to neuronal orientation so difficult to record*
  - *Hypothesis*
    - Relay of the subplate for the thalamic informations to the cortical plate
    - Activation of dendrites of migrating pyramidal cells

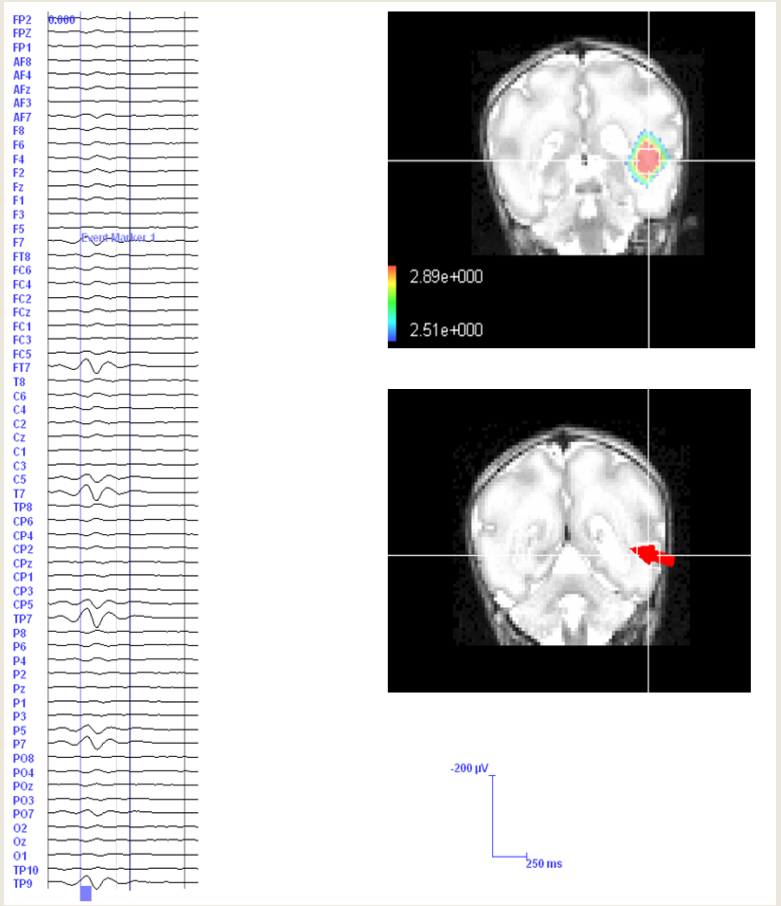


Evolution of the subplate and location of TTA-SW

Role of TTA-SW

- Generator active before the installation of the auditory / language / communication functionalities
- Probable role of functional guidance, neuronal migration, growth, differentiation ... genetically determined *Ayoub et al 2009, Moore et al 2009, 2011*
- Functionality similar to that of the Kölliker's organ, a transient cochlear organ, responsible for endogenous activity essential for the establishment of the functionality of the inner ear

Zhao et al 2009, Kilb et al 2011, Trischt et al 2011



Moyennage et localisation du dipôle des activités thêta gauches

Brain Topography
https://doi.org/10.1007/s10548-019-00713-z

ORIGINAL PAPER

Preterm Modulation of Connectivity by Endogenous Generators: The Theta Temporal Activities in Coalescence with Slow Waves

Azeez Adebimpe[1,2] · Laura Routier[1,3] · Fabrice Wallois[1,3]

Received: 28 January 2019 / Accepted: 16 April 2019

TTA-SW

- As early as 28 wGA , the premature brain is able to discriminate phonemes and voices in specific areas using neural strategies as habituation and mismatch

  ➔ a precocious sophisticated organization of perysylvian areas

Mahmoudzadeh et al. 2013

➔ *Investigate the influence of TTA-SW on the functional connectivity pattern of the early brain*

➔ 64-electrods HD-EEG of 14 healthy preterm infant recorded at 29-32 wGA

➔ Study of the functional connectity segmenting the 6 sec around TTA-SW (period of 2 sec)

- Significant increase of the functional connectivity during TTA-SW

- Left TTA-SW
  - *Significantly increases the functional connectivity between left frontal, temporal and parietal areas*

- Right TTA-SW
  - *A significant increase of FC*

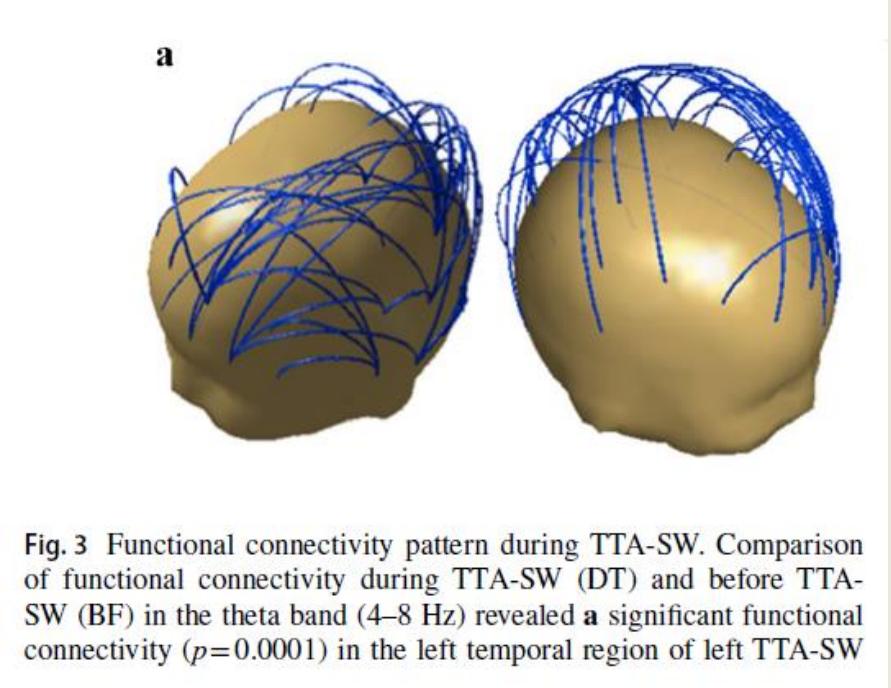


Fig. 3 Functional connectivity pattern during TTA-SW. Comparison of functional connectivity during TTA-SW (DT) and before TTA-SW (BF) in the theta band (4–8 Hz) revealed **a** significant functional connectivity ($p=0.0001$) in the left temporal region of left TTA-SW

Adebimpe et al. 2019

TTA-SW

- Influence on the functional organization of the preterm brain network
- Participate to the prewiring or functional organization of the perisylvian network involved in language and social interactions before the connection to the cortical plate

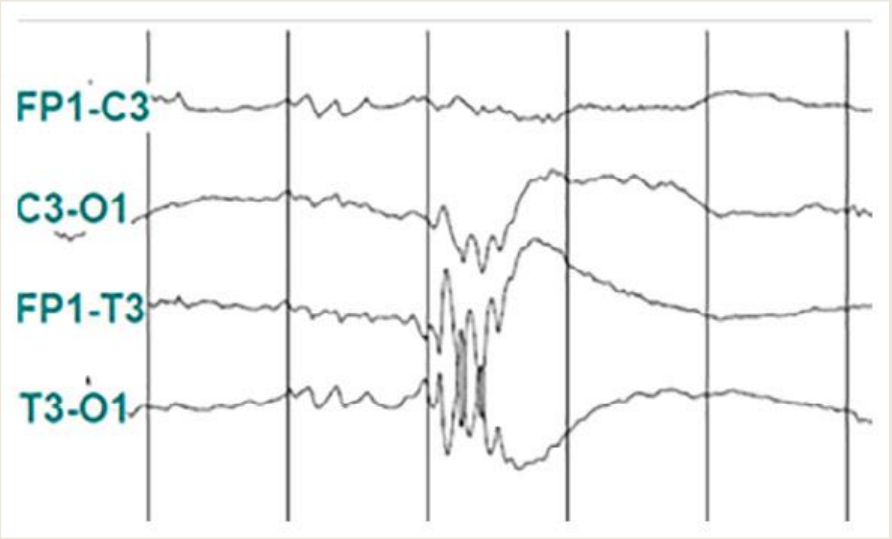
  ➔ *TTA-SW conveys functional messages or neural signals to another targets (optimization and refinement of cortical connections)*
- A repetitive endogenous input involved in the tuning of the perisylvian network
- Relay from a rich local organization of the neural network to a long-distance connectivity between the areas

The intimate relationship between coalescent generators in very premature human newborn brains: Quantifying the coupling of nested endogenous oscillations

Sahar Moghimi[1,2,3] | Azadeh Shadkam[1] | Mahdi Mahmoudzadeh[3,4] | Olivia Calipe[3] | Marine Panzani[3] | Mohammadreza Edalati[1,3] | Maryam Ghorbani[1,2] | Laura Routier[3,4] | Fabrice Wallois[3,4]

TTA-SW = activité thêta temporale en coalescence avec une onde lente

TTA-SW

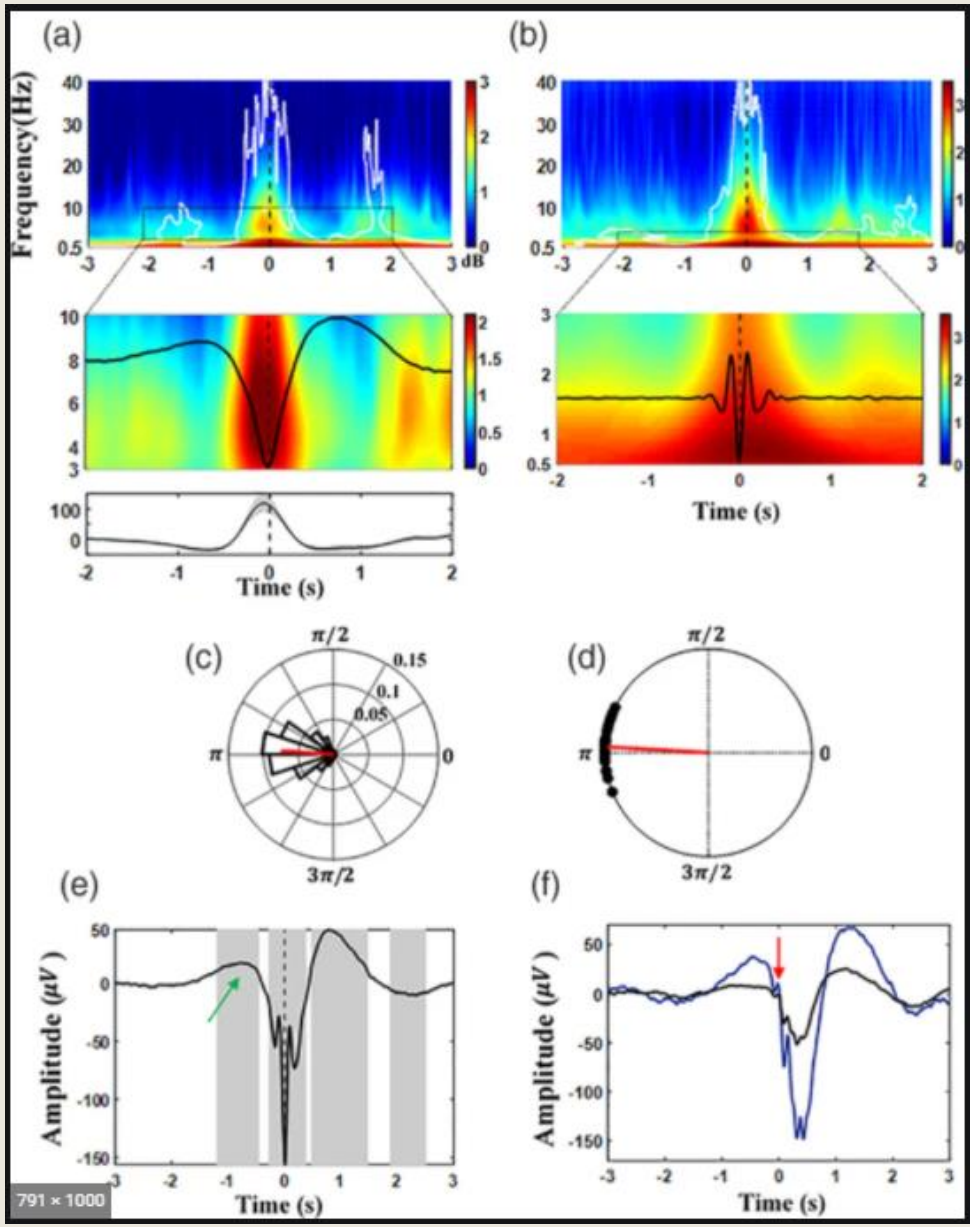


- Important coupling between TTA and SW ?
- Profound functional implications for neural network development ?

➔ 25 EEG of healthy premature neonates recorded at 24-27 wGA

- Development of a tool of automatic detection for TTA and SW separately
  - *Detection techniques adapted from those used to detect sleep oscillations*
  - *Validation of automatic selections by a clinical neurophysiologist*
- Time-frequency analysis to look for a power modulation during TTA and SW
- Phase–amplitude coupling = the moment at which TTA appear in the course of the SW

- TTA power (4–7.5 Hz) modulated during the SW
- TTA power
  - ↑ *during the descending phase of the SW*
  - *Peaked during the SW trough (slightly preceding the SW trough)*
  - ↓ *during the positive slope*
  - *Disappeared during the SW peak*
- A high temporal precision of the TTA power nesting within SW cycles (slightly before the SW trough) for all events



Moghimi et al. 2020

Conclusions TTA-SW

- A deep location in the planum temporale
- A very precise temporal relationship with an orchestration of TTA by SW
- Precise phase amplitude coupling between 2 oscillators (TTA and SW) from 24 wGA
- An early endogenous neurobiomarker composed of 2 oscillators which are able to reinforce the functionnal connectivity of the perisylvian areas

➔ Complexity and relative maturity of the initial mechanisms

Hypothesis

- The fined-tune temporal relationship between TTA and SW is a marker of endogenous interactions between the subplate, the cortical plate and thalamic afferents

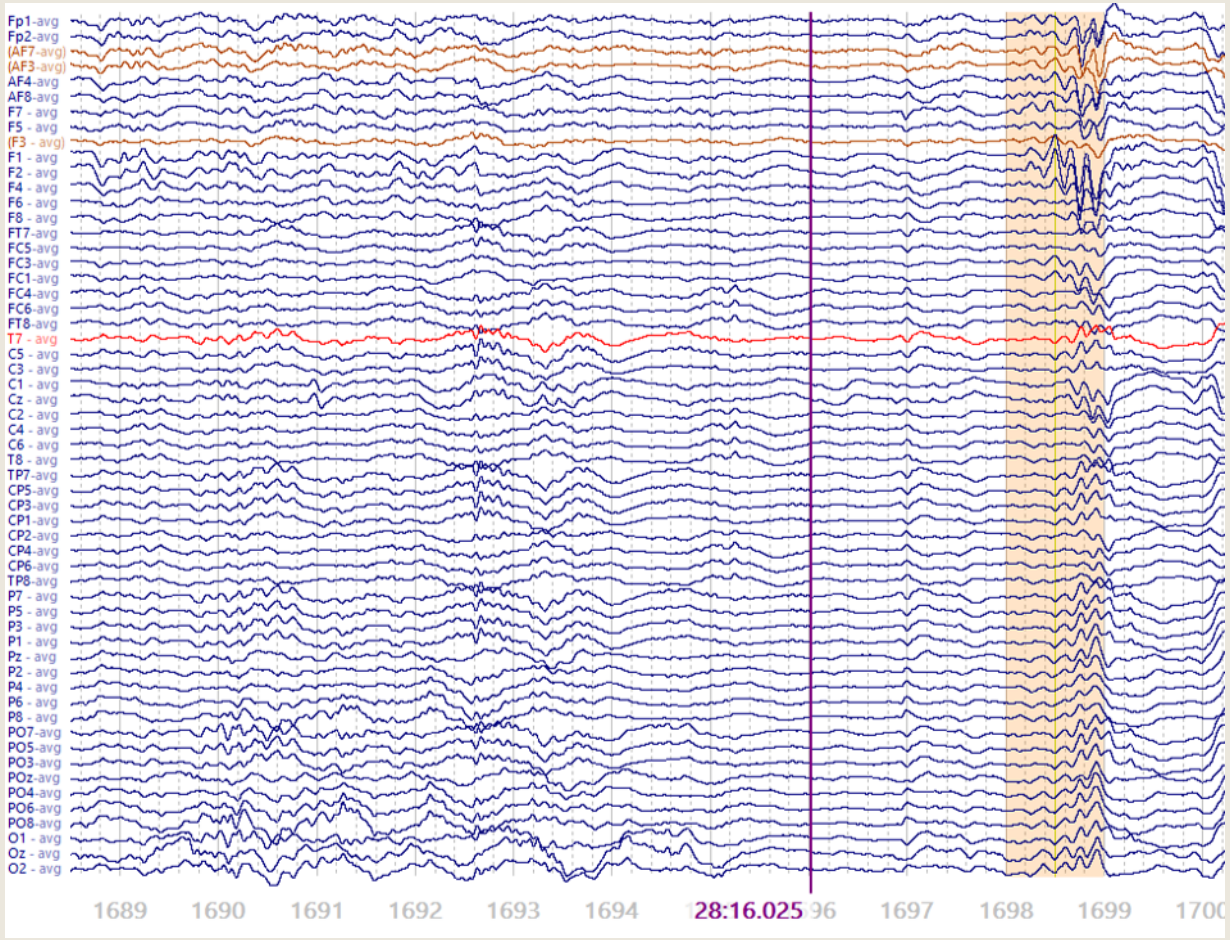
- TTA-SW paticipates to the early development of the neural circuits corresponding to later processing if sensory information

➔ Preparation of the cortical sensory awareness

- Similar pattern of "_TA-SW" in other regions
  - *generic activity preparing the implementation, the awareness of sensoriality?*

- A lot of neurodevelopmental disorders in premature infants
  - *Sensory motor, cognitive, language disorder, ASD, ADHD….*
  - *Caused by a precocious disturbed neuronal wiring consistent with a disrupted functional organization*

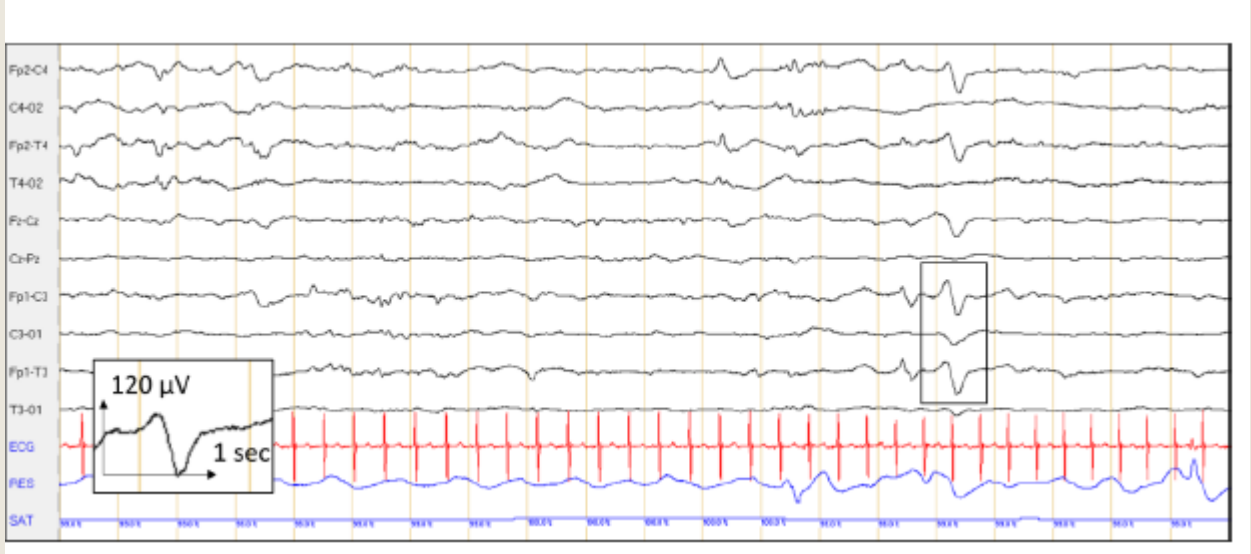
- A better predictive evaluation studying the phase amplitude relationship?



TFA 30wGA

WHY THE FRONTAL LOBE?

FST



- Frontal sharp transient (FST) = « encoche frontale »
- Biphasic activities in the prefrontal regions
- Specific strong frontal transient activity 35-43 wGA
- Mostly seen during sleep
- Clinically accepted that the presence of FST at term confers a favorable neurological outcome.
  - *The high predictive value of this neurobiomarker was attributed to it in view of its absence in extremely abnormal EEGs*

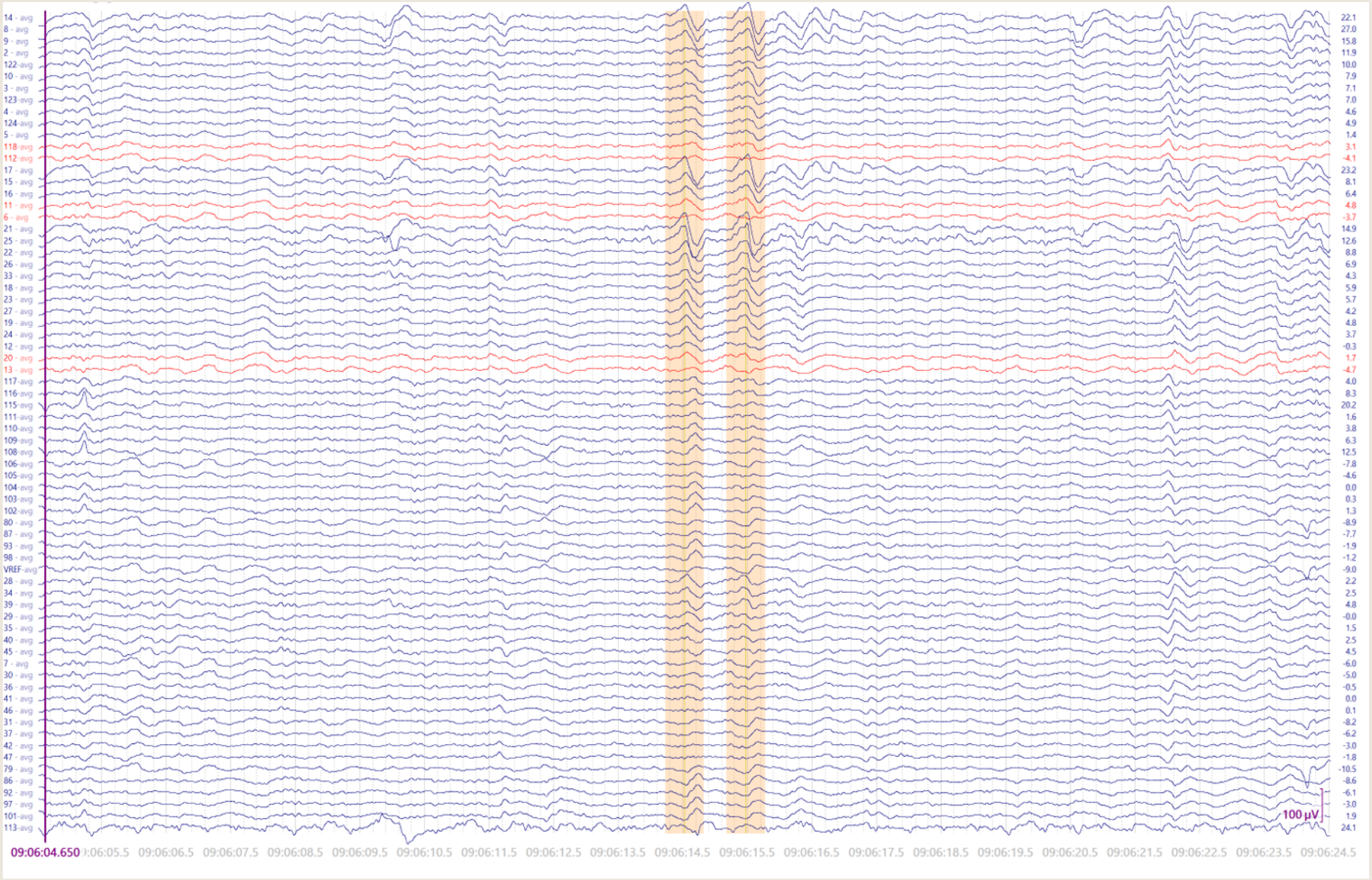
Arfel et al. 1977, Monod et al. 1960

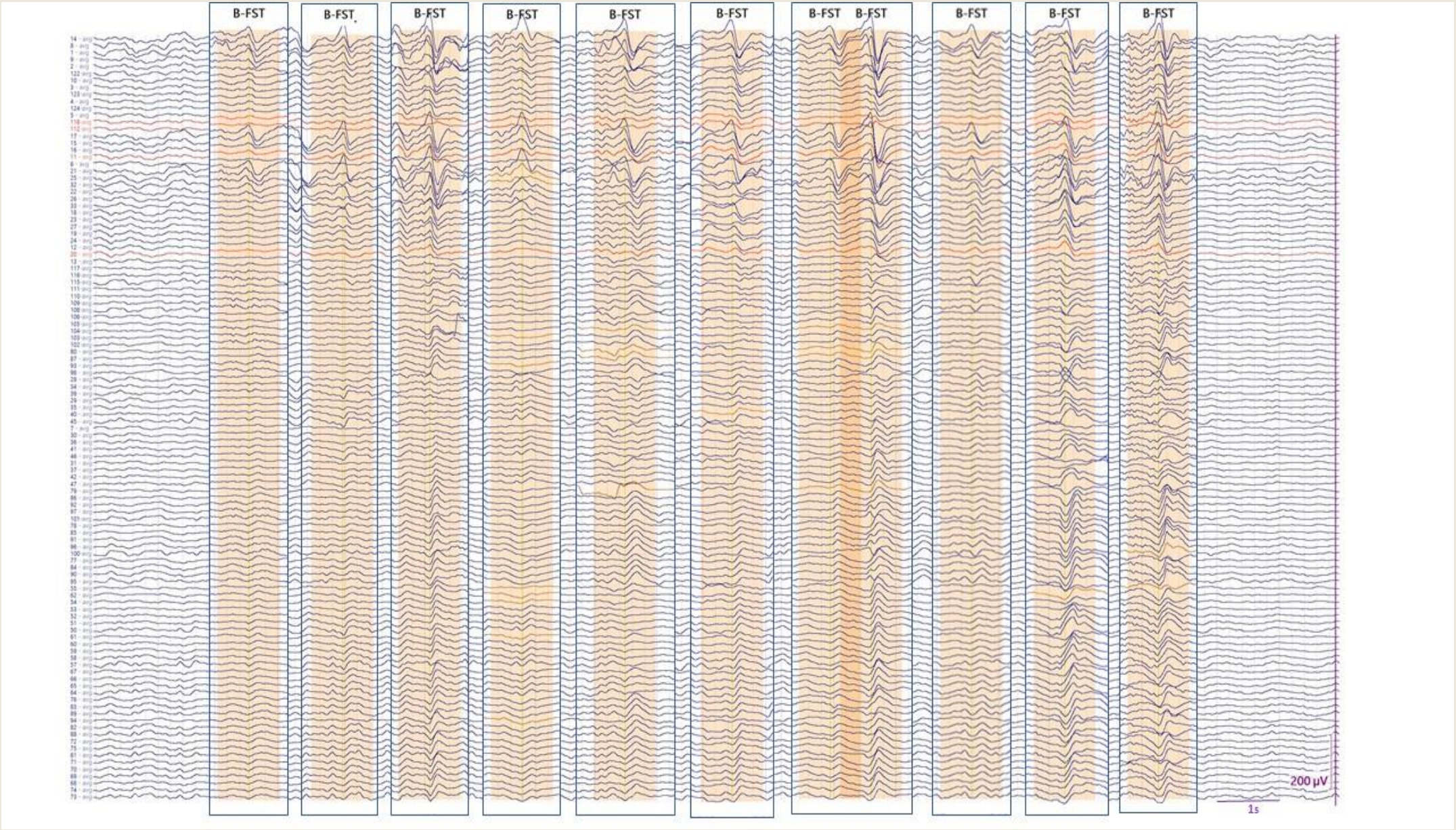
- FST's functionality? Generator?

➔ endogen or senrory-driven transient activities?

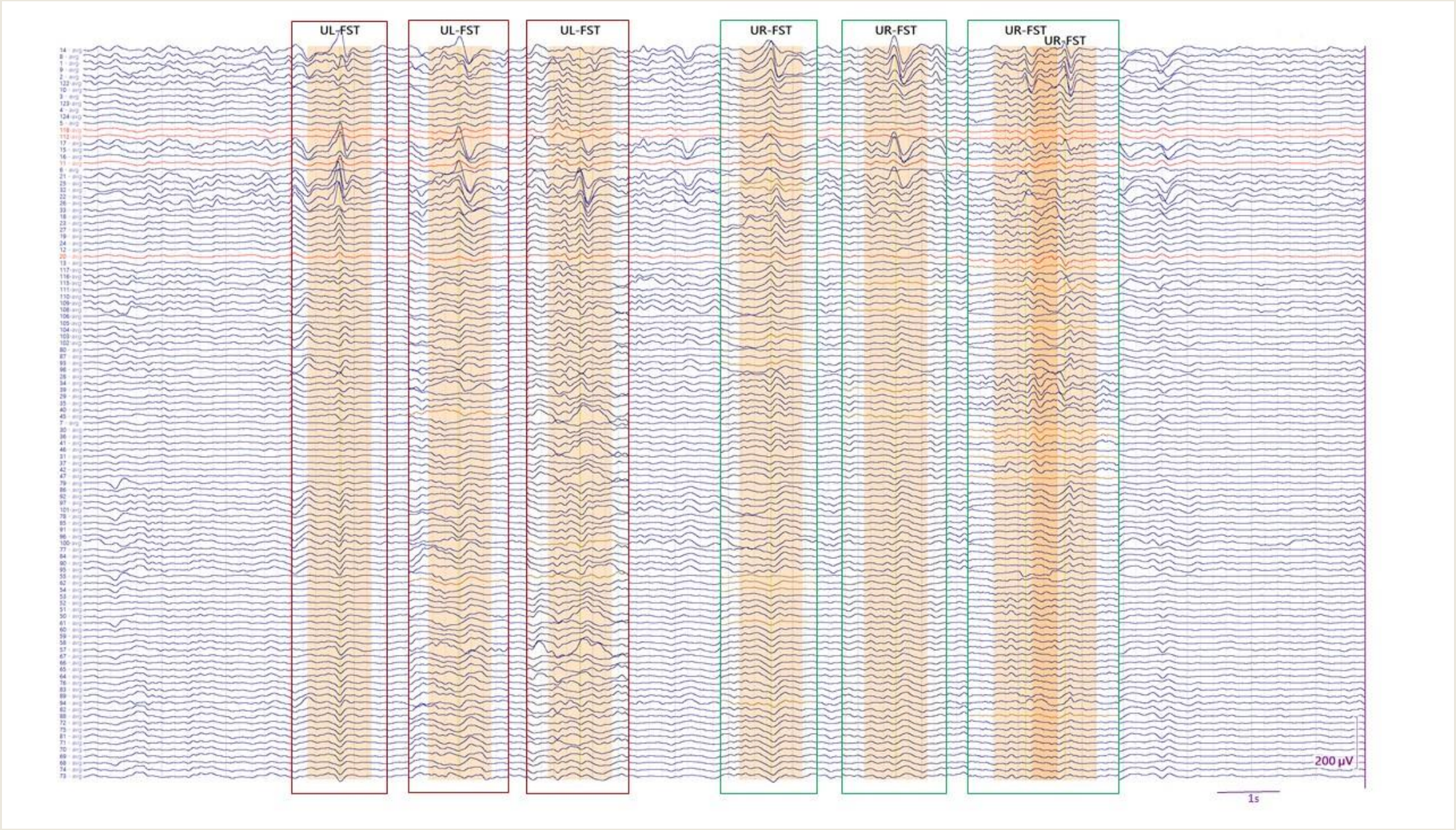
➔ specific to the development of the frontal cortex?

- 128 electrods HD-EEG of 20 healthy newborn borned at term
- 425 selected FST

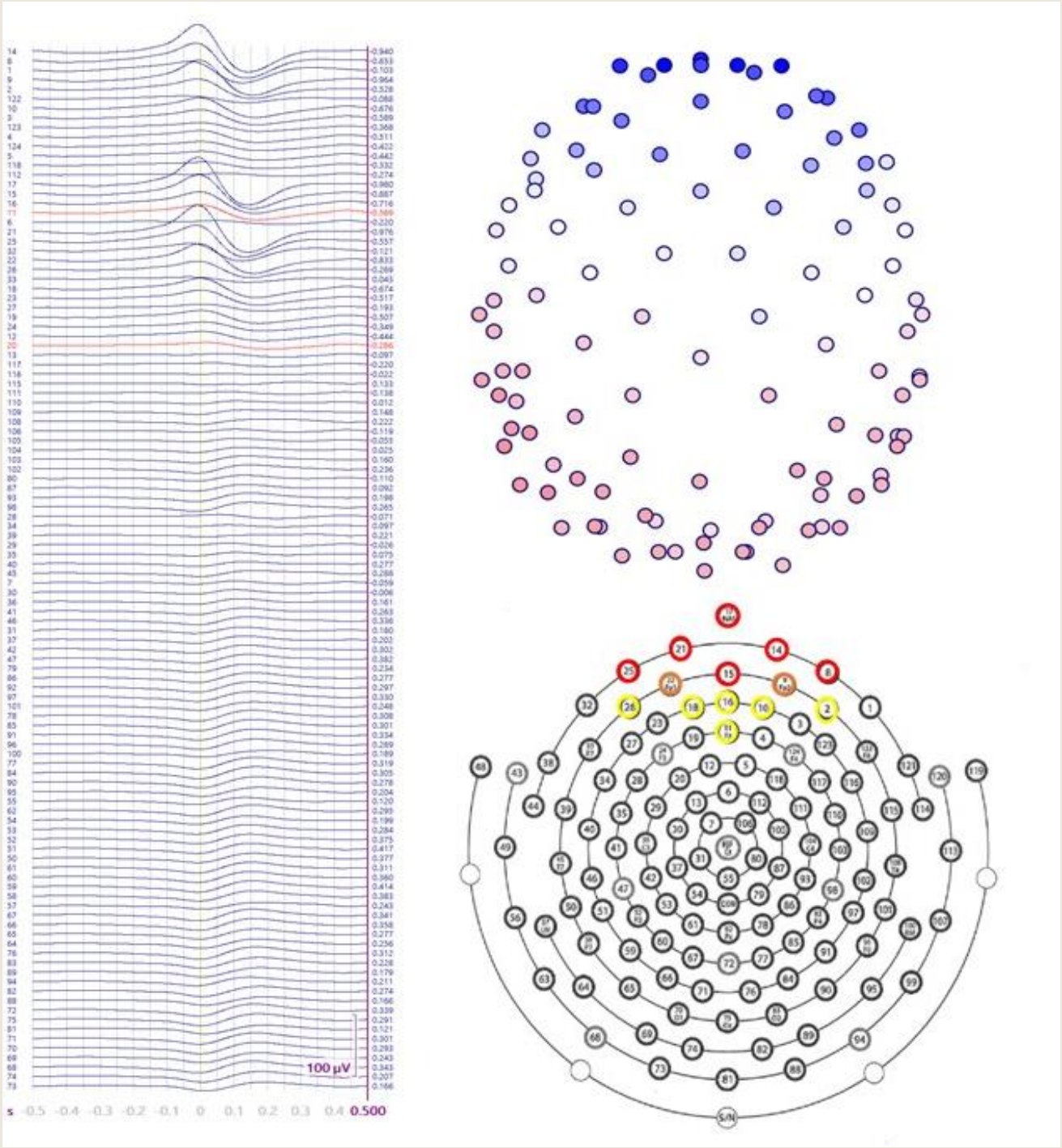




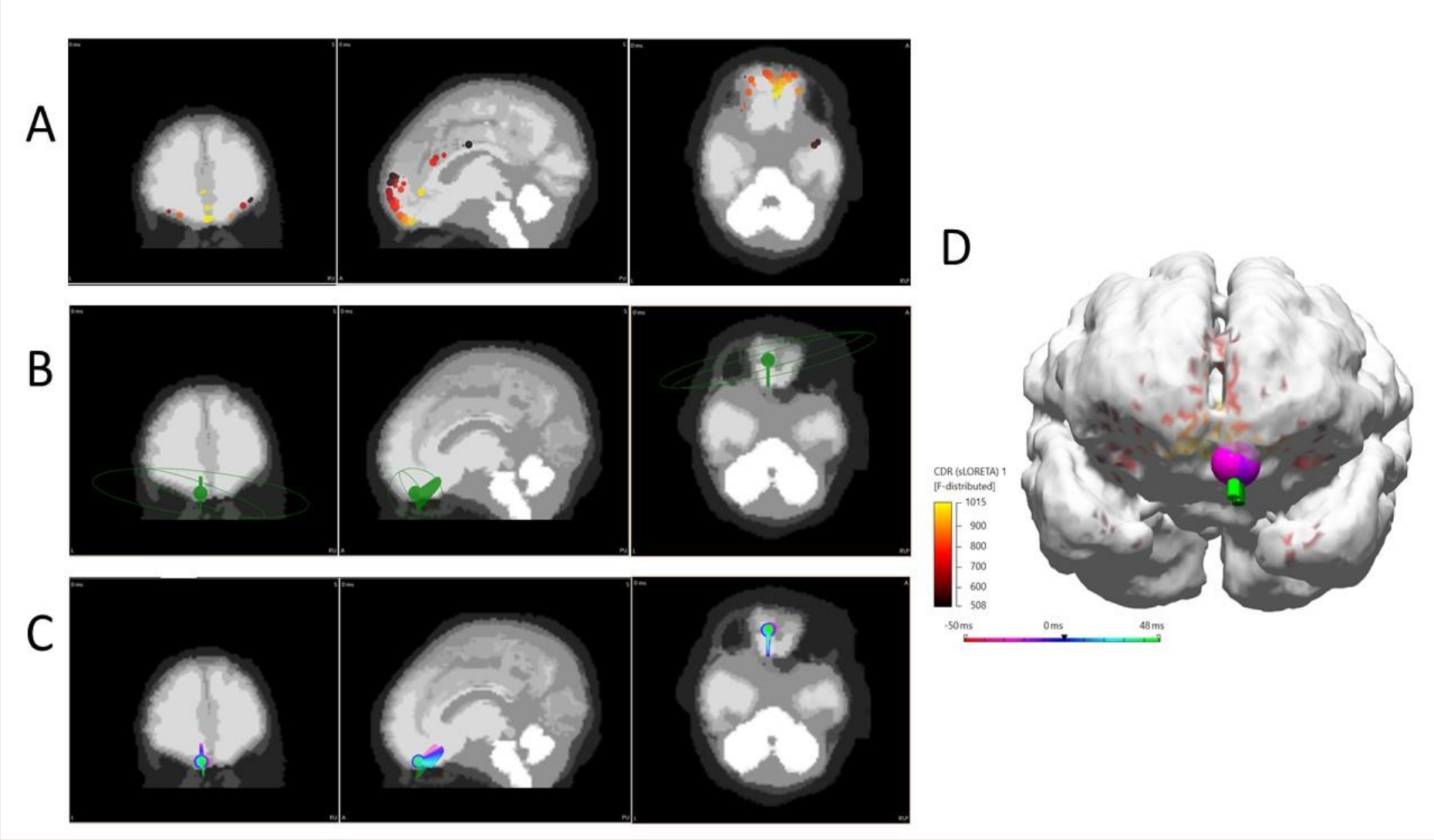
Bilateral FST



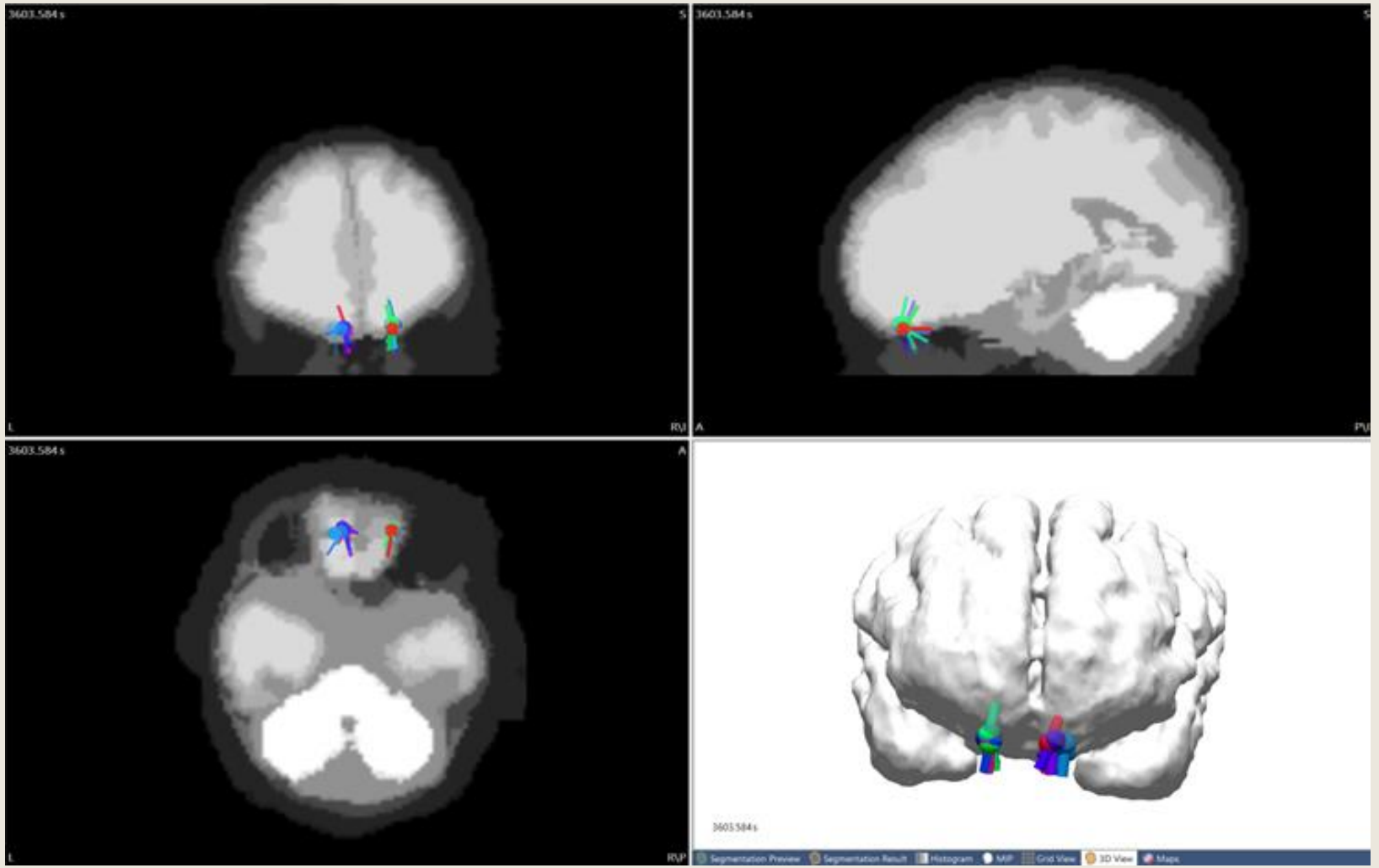
Unilateral FST



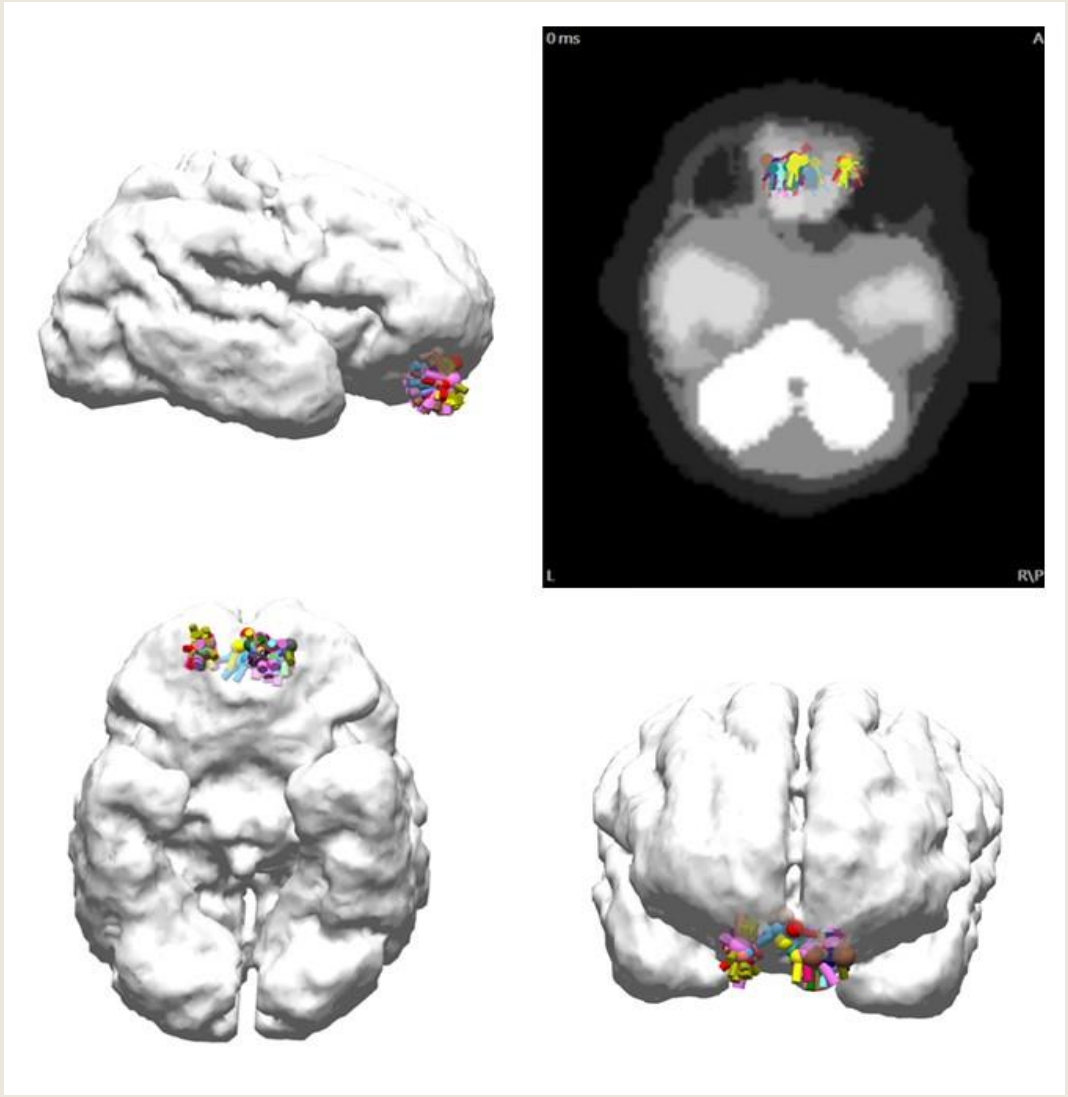
Grand averaging of bilateral FST, amplitude cartography at negative peak and electrodes concerned by it.



Location of grand averaging B-FSTs



Mean location obtained from the average activities per patient



All B-FST dipole obtained from the averaging of each patient with one dipole‘s colour by patient.

Location in the orbito-frontal cortex?

In the olfactory bulbs?

Involvement in olfaction?

- But very early organization of the olfactory system during T2
- No clear and obvious link between breathing and the occurrence of FST

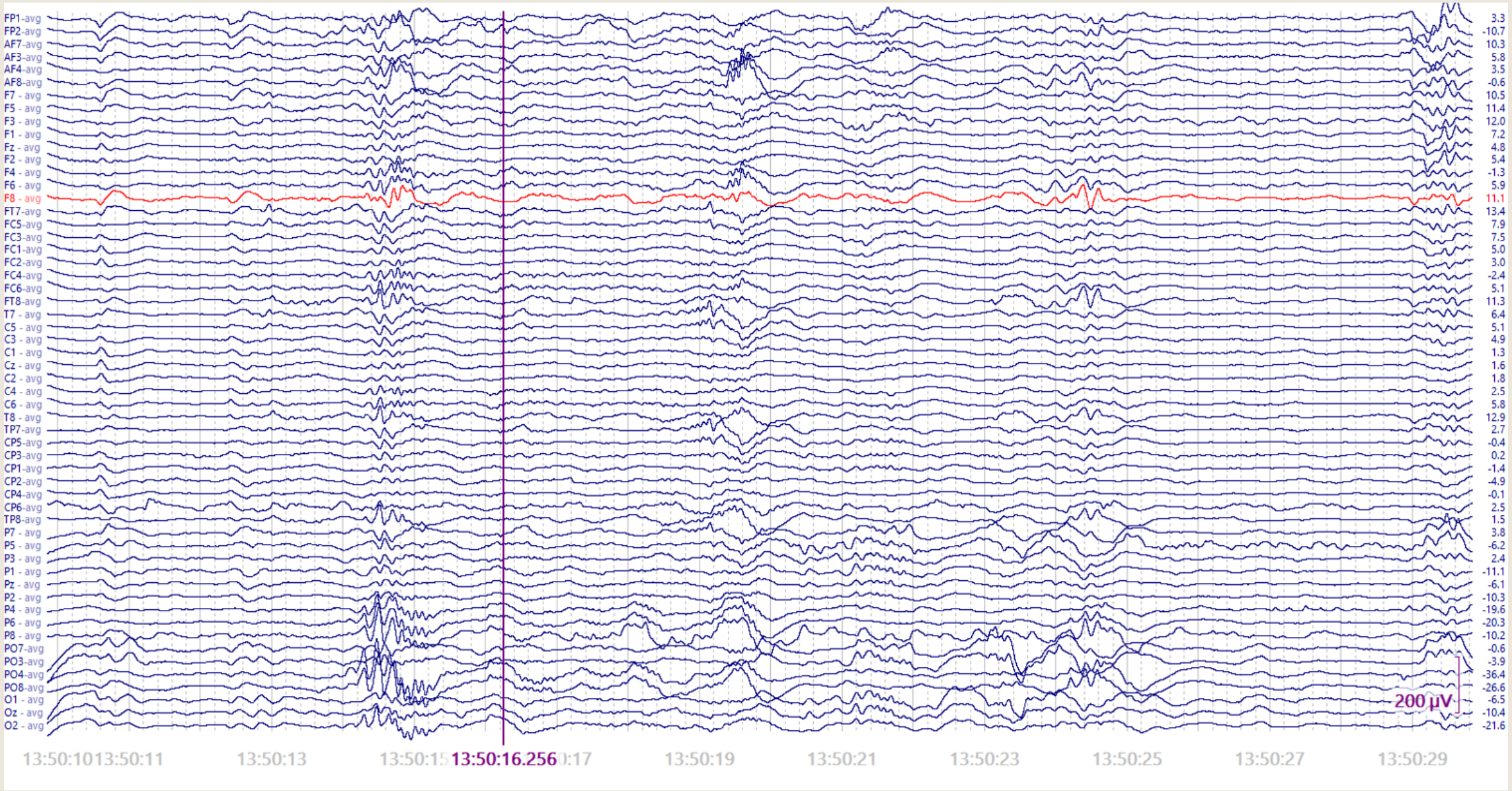
Occurrence around the term

- Very strong activities, "resistant" to pathological mechanisms
- No maturation the FST over time
- Participate in the survival of the child?
- Impact on memorizing and learning smells ?

➔ *Work in progress !*

ACTIVITIES NOT SEEN IN LD-EEG OFFERED BY HD-EEG

Richness of HD-EEG…


FP1-avg
FP2-avg
AF7-avg
AF3-avg
AF4-avg
AF8-avg
F7 - avg
F5 - avg
F3 - avg
F1 - avg
Fz - avg
F2 - avg
F4 - avg
F6 - avg
F8 - avg
FT7-avg
FC5-avg
FC3-avg
FC1-avg
FC2-avg
FC4-avg
FC6-avg
FT8-avg
T7 - avg
C5 - avg
C3 - avg
C1 - avg
Cz - avg
C2 - avg
C4 - avg
C6 - avg
T8 - avg
TP7-avg
CP5-avg
CP3-avg
CP1-avg
CP2-avg
CP4-avg
CP6-avg
TP8-avg
P7 - avg
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P3 - avg
P1 - avg
Pz - avg
P2 - avg
P4 - avg
P6 - avg
P8 - avg
PO7-avg
PO3-avg
PO4-avg
PO8-avg
O1 - avg
Oz - avg
O2 - avg
3.3
-10.7
10.3
5.8
3.5
-0.6
10.5
11.4
12.0
7.2
4.8
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-1.3
5.9
11.1
13.4
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0.2
-1.4
-4.9
-0.1
2.5
1.5
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-6.2
2.4
-11.1
-6.1
-10.3
-19.6
-20.3
-10.2
-0.6
-3.9
-36.4
-26.6
-6.5
-10.4
-21.6
200 µV
13:50:10
13:50:11
13:50:13
13:50:15
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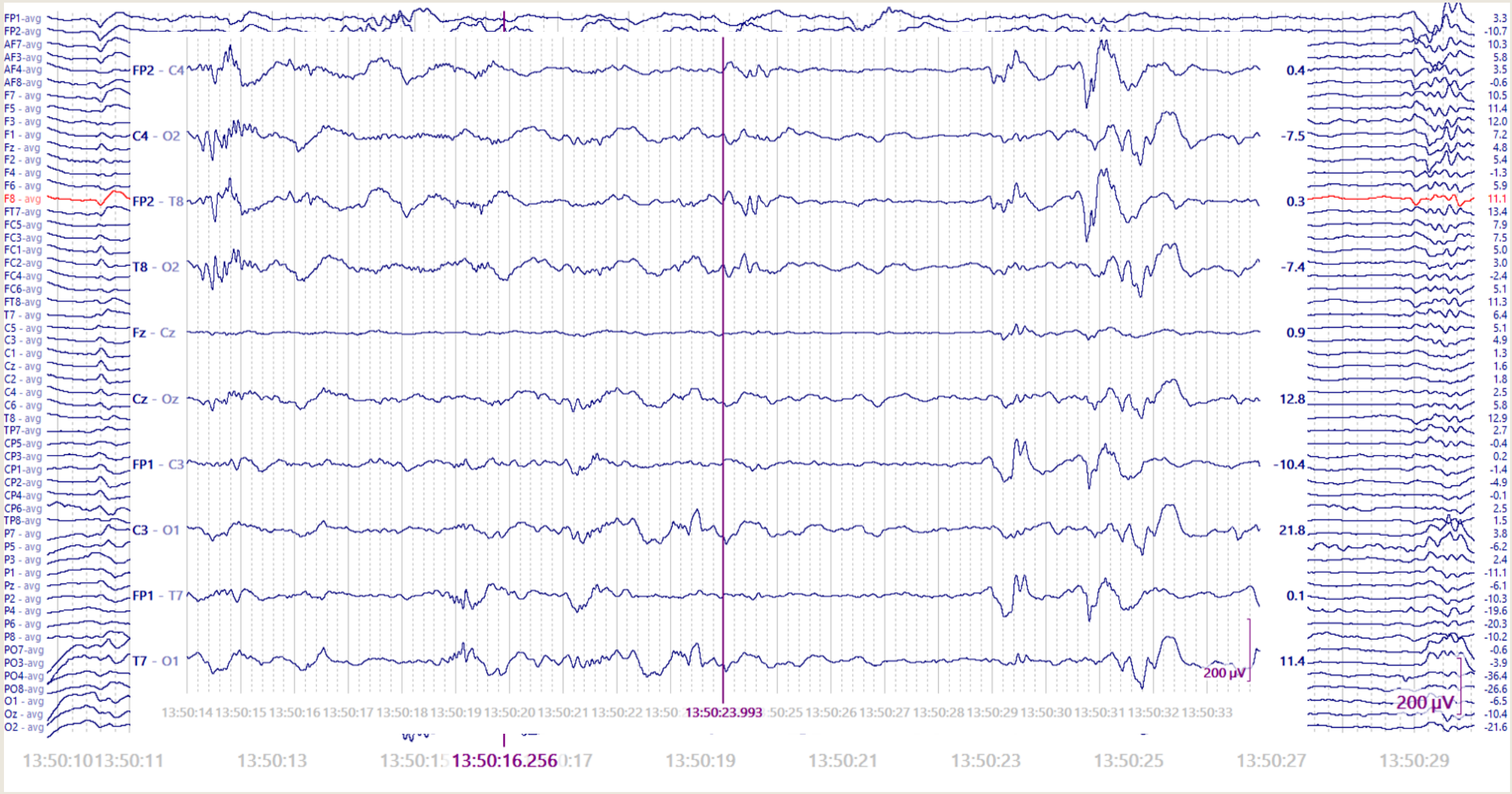
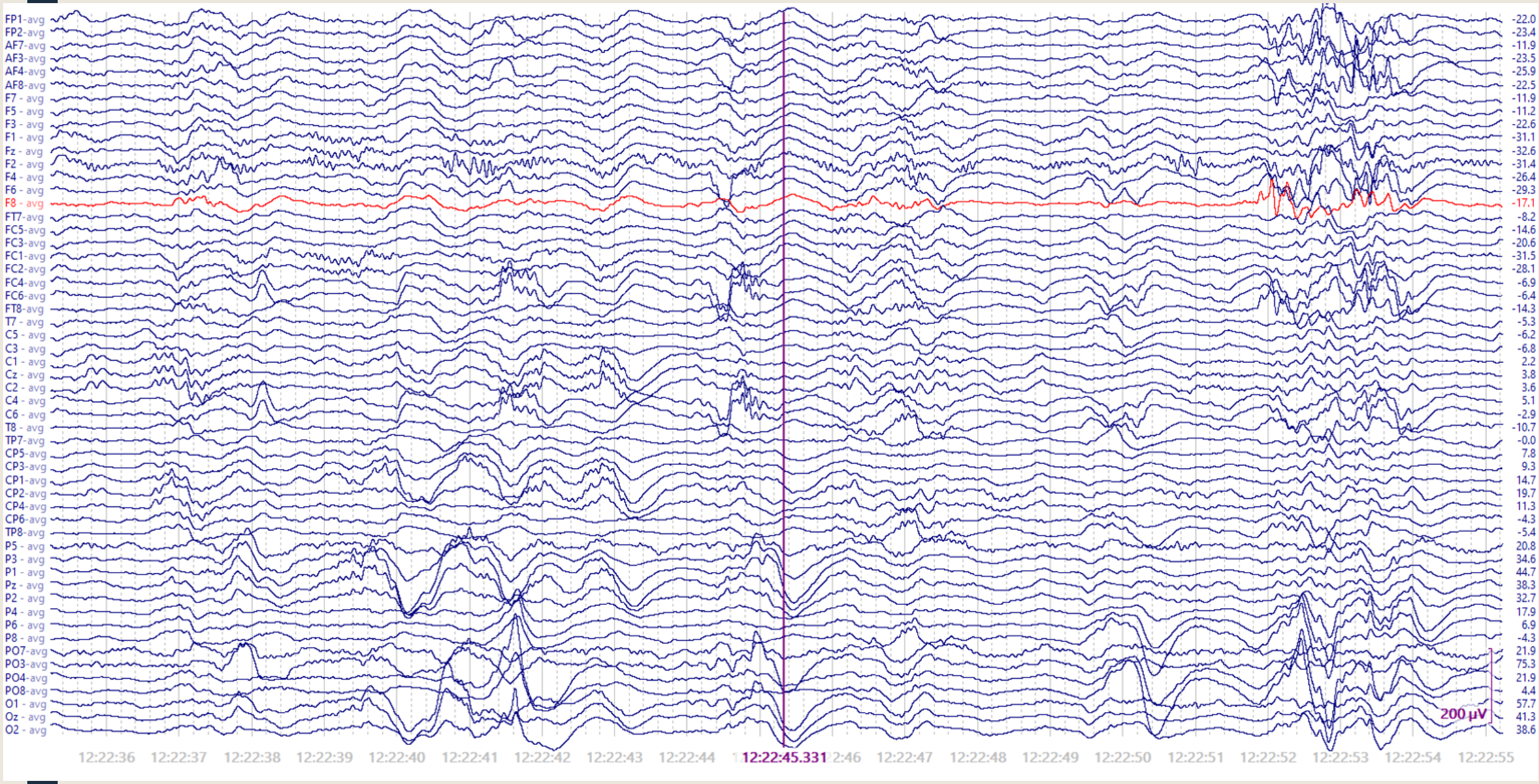
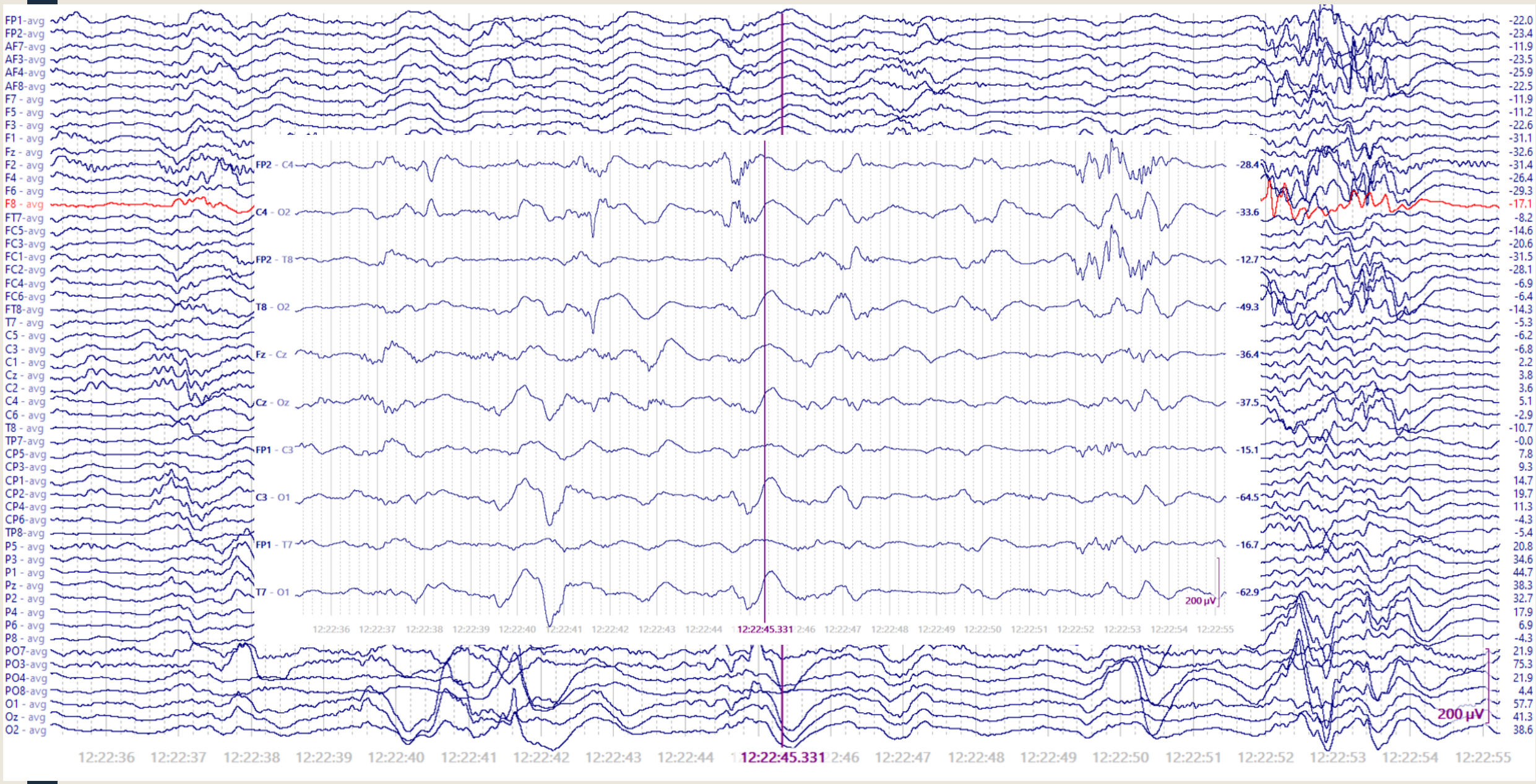
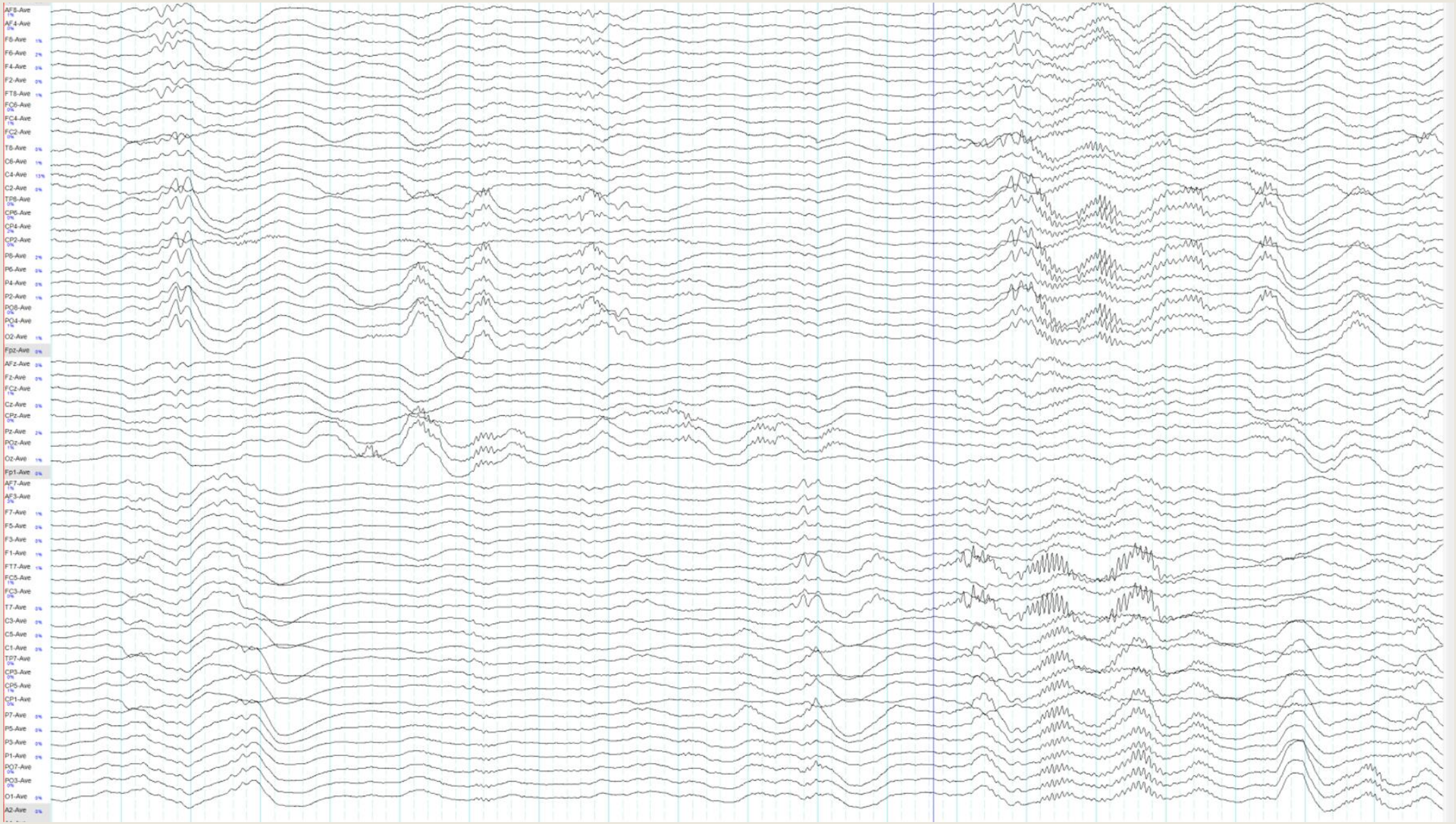
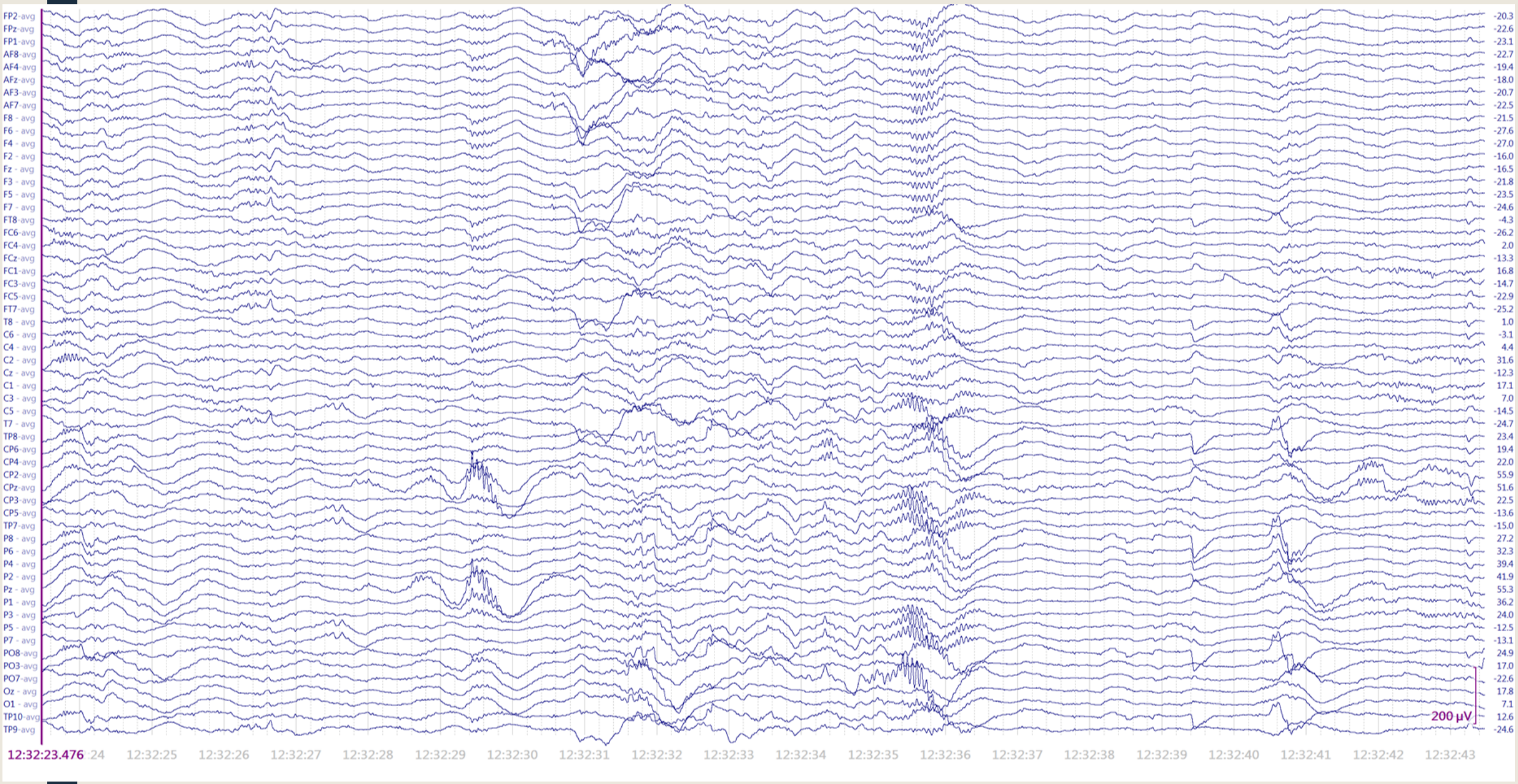

FP1-avg
FP2-avg
AF7-avg
AF3-avg
AF4-avg
AF8-avg
F7 - avg
F5 - avg
F3 - avg
F1 - avg
Fz - avg
F2 - avg
F4 - avg
F6 - avg
F8 - avg
FT7-avg
FC5-avg
FC3-avg
FC1-avg
FC2-avg
FC4-avg
FC6-avg
FT8-avg
T7 - avg
C5 - avg
C3 - avg
C1 - avg
Cz - avg
C2 - avg
C4 - avg
C6 - avg
T8 - avg
TP7-avg
CP5-avg
CP3-avg
CP1-avg
CP2-avg
CP4-avg
CP6-avg
TP8-avg
P7 - avg
P5 - avg
P3 - avg
P1 - avg
Pz - avg
P2 - avg
P4 - avg
P6 - avg
P8 - avg
PO7-avg
PO3-avg
PO4-avg
PO8-avg
O1 - avg
Oz - avg
O2 - avg
FP2 - C4
C4 - O2
FP2 - T8
T8 - O2
Fz - Cz
Cz - Oz
FP1 - C3
C3 - O1
FP1 - T7
T7 - O1
0.4
-7.5
0.3
-7.4
0.9
12.8
-10.4
21.8
0.1
11.4
200 µV
200 µV
13:50:14 13:50:15 13:50:16 13:50:17 13:50:18 13:50:19 13:50:20 13:50:21 13:50:22 13:50 13:50:23.993 50:25 13:50:26 13:50:27 13:50:28 13:50:29 13:50:30 13:50:31 13:50:32 13:50:33
13:50:10 13:50:11 13:50:13 13:50:15 13:50:16.256 0:17 13:50:19 13:50:21 13:50:23 13:50:25 13:50:27 13:50:29


FP1-avg
FP2-avg
AF7-avg
AF3-avg
AF4-avg
AF8-avg
F7 - avg
F5 - avg
F3 - avg
F1 - avg
Fz - avg
F2 - avg
F4 - avg
F6 - avg
F8 - avg
FT7-avg
FC5-avg
FC3-avg
FC1-avg
FC2-avg
FC4-avg
FC6-avg
FT8-avg
T7 - avg
C5 - avg
C3 - avg
C1 - avg
Cz - avg
C2 - avg
C4 - avg
C6 - avg
T8 - avg
TP7-avg
CP5-avg
CP3-avg
CP1-avg
CP2-avg
CP4-avg
CP6-avg
TP8-avg
P5 - avg
P3 - avg
P1 - avg
Pz - avg
P2 - avg
P4 - avg
P6 - avg
P8 - avg
PO7-avg
PO3-avg
PO4-avg
PO8-avg
O1 - avg
Oz - avg
O2 - avg
-22.0
-23.4
-11.9
-23.5
-25.9
-22.5
-11.9
-11.2
-22.6
-31.1
-32.6
-31.4
-26.4
-29.3
-17.1
-8.2
-14.6
-20.6
-31.5
-28.1
-6.9
-6.4
-14.3
-5.3
-6.2
-6.8
2.2
3.8
3.6
5.1
-2.9
-10.7
-0.0
7.8
9.3
14.7
19.7
11.3
-4.3
-5.4
20.8
34.6
44.7
38.3
32.7
17.9
6.9
-4.3
21.9
75.3
21.9
4.4
57.7
41.3
38.6
200 µV
12:22:36
12:22:37
12:22:38
12:22:39
12:22:40
12:22:41
12:22:42
12:22:43
12:22:44
12:22:45.331
12:22:46
12:22:47
12:22:48
12:22:49
12:22:50
12:22:51
12:22:52
12:22:53
12:22:54
12:22:55


FP1-avg
FP2-avg
AF7-avg
AF3-avg
AF4-avg
AF8-avg
F7 - avg
F5 - avg
F3 - avg
F1 - avg
Fz - avg
F2 - avg
F4 - avg
F6 - avg
F8 - avg
FT7-avg
FC5-avg
FC3-avg
FC1-avg
FC2-avg
FC4-avg
FC6-avg
FT8-avg
T7 - avg
C5 - avg
C3 - avg
C1 - avg
Cz - avg
C2 - avg
C4 - avg
C6 - avg
T8 - avg
TP7-avg
CP5-avg
CP3-avg
CP1-avg
CP2-avg
CP4-avg
CP6-avg
TP8-avg
P5 - avg
P3 - avg
P1 - avg
Pz - avg
P2 - avg
P4 - avg
P6 - avg
P8 - avg
PO7-avg
PO3-avg
PO4-avg
PO8-avg
O1 - avg
Oz - avg
O2 - avg
FP2 - C4
C4 - O2
FP2 - T8
T8 - O2
Fz - Cz
Cz - Oz
FP1 - C3
C3 - O1
FP1 - T7
T7 - O1
-28.4
-33.6
-12.7
-49.3
-36.4
-37.5
-15.1
-64.5
-16.7
-62.9
200 µV
12:22:36 12:22:37 12:22:38 12:22:39 12:22:40 12:22:41 12:22:42 12:22:43 12:22:44 12:22:45.331 12:22:46 12:22:47 12:22:48 12:22:49 12:22:50 12:22:51 12:22:52 12:22:53 12:22:54 12:22:55
-22.0
-23.4
-11.9
-23.5
-25.9
-22.5
-11.9
-11.2
-22.6
-31.1
-32.6
-31.4
-26.4
-29.3
-17.1
-8.2
-14.6
-20.6
-31.5
-28.1
-6.9
-6.4
-14.3
-5.3
-6.2
-6.8
2.2
3.8
3.6
5.1
-2.9
-10.7
-0.0
7.8
9.3
14.7
19.7
11.3
-4.3
-5.4
20.8
34.6
44.7
38.3
32.7
17.9
6.9
-4.3
21.9
75.3
21.9
4.4
57.7
41.3
38.6
200 µV
12:22:36 12:22:37 12:22:38 12:22:39 12:22:40 12:22:41 12:22:42 12:22:43 12:22:44 12:22:45.331 12:22:46 12:22:47 12:22:48 12:22:49 12:22:50 12:22:51 12:22:52 12:22:53 12:22:54 12:22:55


AF8-Ave
AF4-Ave
F8-Ave
F6-Ave
F4-Ave
F2-Ave
FT8-Ave
FC6-Ave
FC4-Ave
FC2-Ave
T8-Ave
C6-Ave
C4-Ave
C2-Ave
TP8-Ave
CP6-Ave
CP4-Ave
CP2-Ave
P6-Ave
P6-Ave
P4-Ave
P2-Ave
PO8-Ave
PO4-Ave
O2-Ave
Fpz-Ave
AFz-Ave
Fz-Ave
FCz-Ave
Cz-Ave
CPz-Ave
Pz-Ave
POz-Ave
Oz-Ave
Fp1-Ave
AF7-Ave
AF3-Ave
F7-Ave
F5-Ave
F3-Ave
F1-Ave
FT7-Ave
FC5-Ave
FC3-Ave
T7-Ave
C3-Ave
C5-Ave
C1-Ave
TP7-Ave
CP3-Ave
CP5-Ave
CP1-Ave
P7-Ave
P5-Ave
P3-Ave
P1-Ave
PO7-Ave
PO3-Ave
O1-Ave
A2-Ave


FP2-avg
FPz-avg
FP1-avg
AF8-avg
AF4-avg
AFz-avg
AF3-avg
AF7-avg
F8 - avg
F6 - avg
F4 - avg
F2 - avg
Fz - avg
F3 - avg
F5 - avg
F7 - avg
FT8-avg
FC6-avg
FC4-avg
FCz-avg
FC1-avg
FC3-avg
FC5-avg
FT7-avg
T8 - avg
C6 - avg
C4 - avg
C2 - avg
Cz - avg
C1 - avg
C3 - avg
C5 - avg
T7 - avg
TP8-avg
CP6-avg
CP4-avg
CP2-avg
CPz-avg
CP3-avg
CP5-avg
TP7-avg
P8 - avg
P6 - avg
P4 - avg
P2 - avg
Pz - avg
P1 - avg
P3 - avg
P5 - avg
P7 - avg
PO8-avg
PO3-avg
PO7-avg
Oz - avg
O1 - avg
TP10-avg
TP9-avg
-20.3
-22.6
-23.1
-22.7
-19.4
-18.0
-20.7
-22.5
-21.5
-27.6
-27.0
-16.0
-16.5
-21.8
-23.5
-24.6
-4.3
-26.2
2.0
-13.3
16.8
-14.7
-22.9
-25.2
1.0
-3.1
4.4
31.6
-12.3
17.1
7.0
-14.5
-24.7
23.4
19.4
22.0
55.9
51.6
22.5
-13.6
-15.0
27.2
32.3
39.4
41.9
55.3
36.2
24.0
-12.5
-13.1
24.9
17.0
-22.6
17.8
7.1
12.6
-24.6
200 µV
12:32:23.476
24
12:32:25
12:32:26
12:32:27
12:32:28
12:32:29
12:32:30
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12:32:42
12:32:43

CONCLUSIONS

- The new world of HD-EEG
- Closed future of profound modifications in interpretation of EEG
- Development of new criteria that could better predict the neurodevelopmental outcome (phase coupling, connectivity etc …)
- Use of artificial intelligence because of the richness of HD-EEG activities
- The better the comprehension of the physiological mechanisms, the better the clinical and predictive evaluation

Still so much to discover …

Let’s go!

Thank you!