Inserm
Institut national
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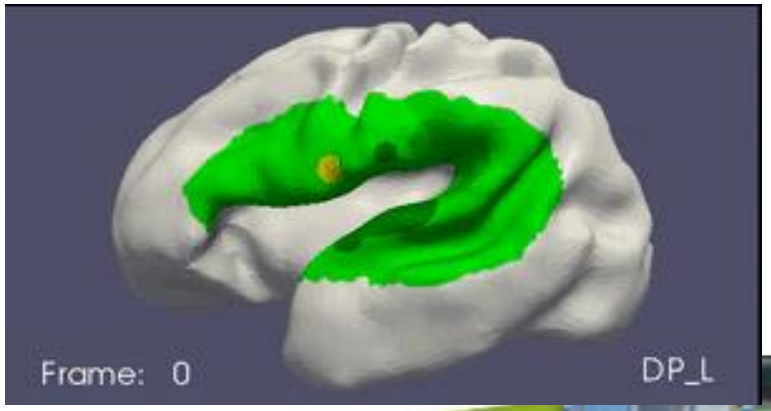
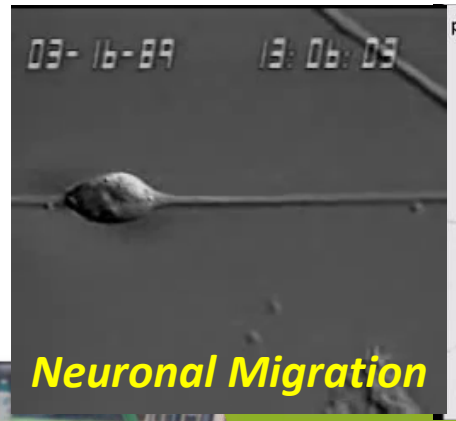
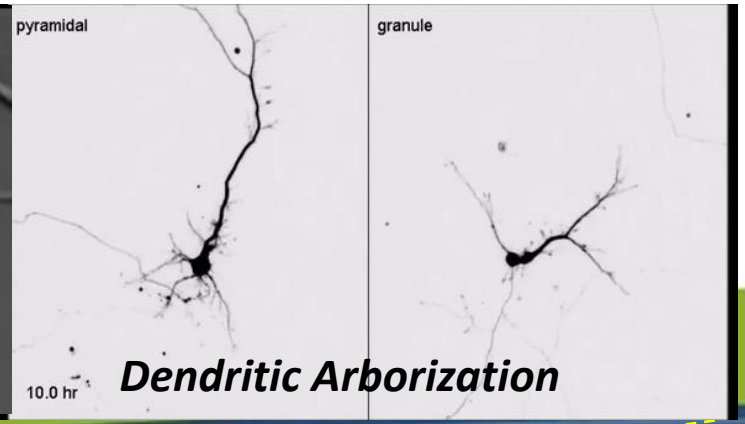
UNIVERSITÉ de Picardie Jules Verne

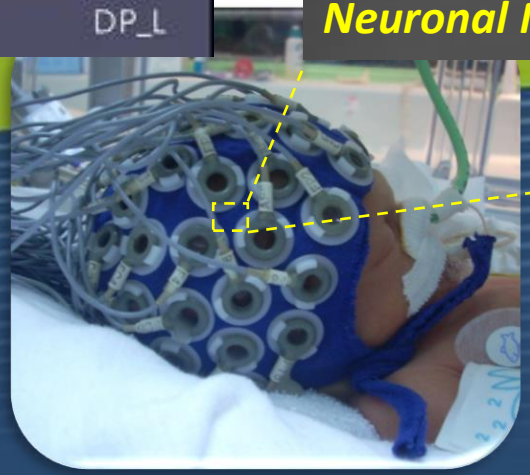
CHU AMIENS PICARDIE

GRAMFC
Groupe de Recherche sur l'Analyse Multimodale de la Fonction Cérébrale
INSERM U1105







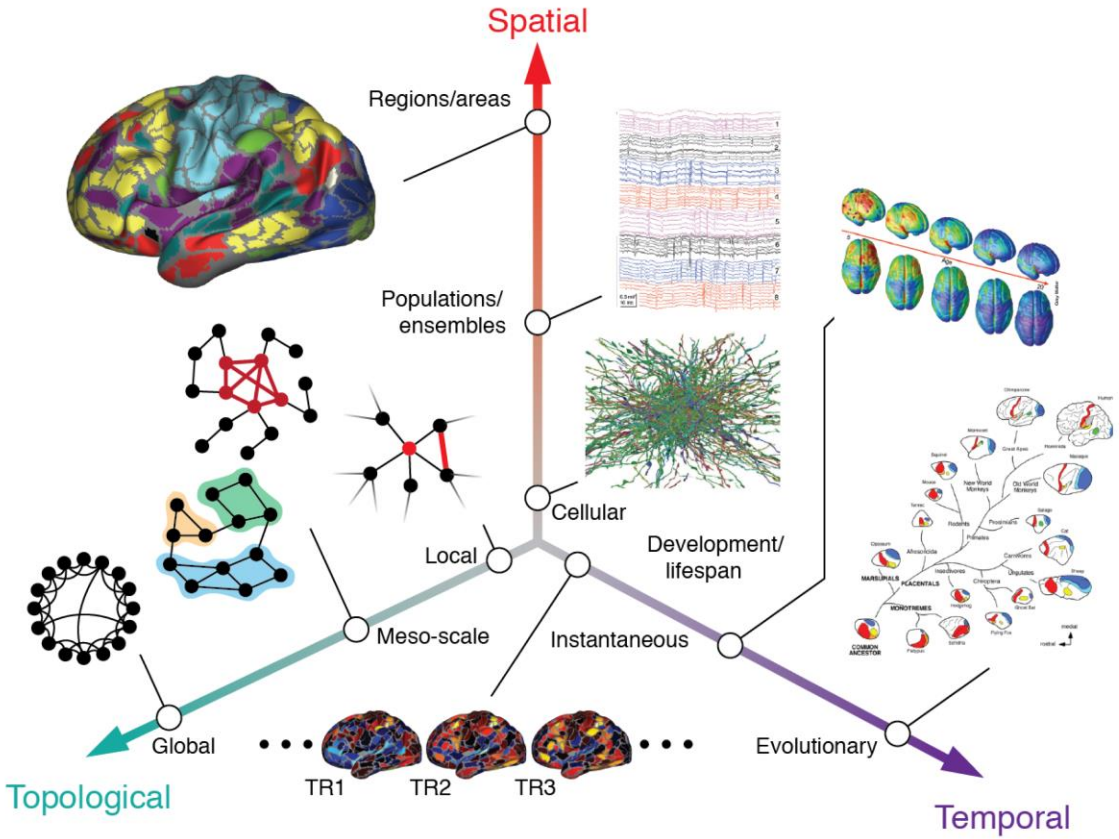


Multimodal neuroimaging of developing brain

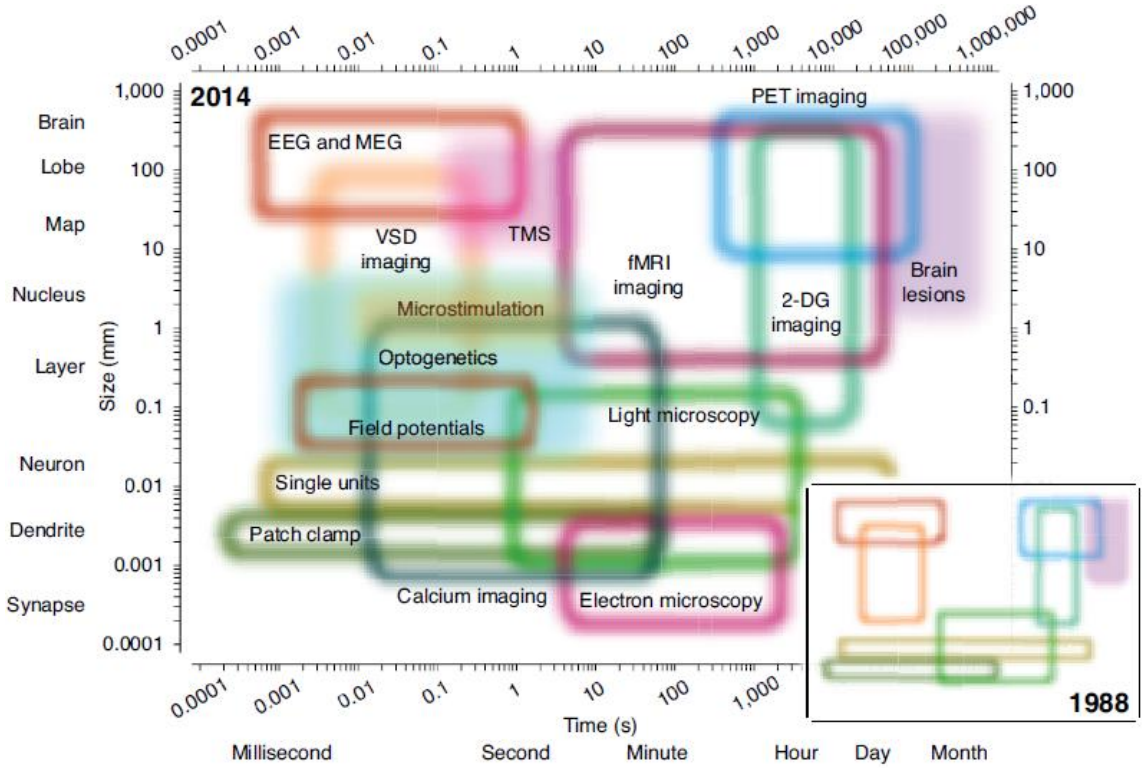
Mahdi Mahmoud Zadeh (Ph.D. , HDR)

University Hospital of Amiens, France

MULTI-SCALE BRAIN



betzel and bassett 2017 NI

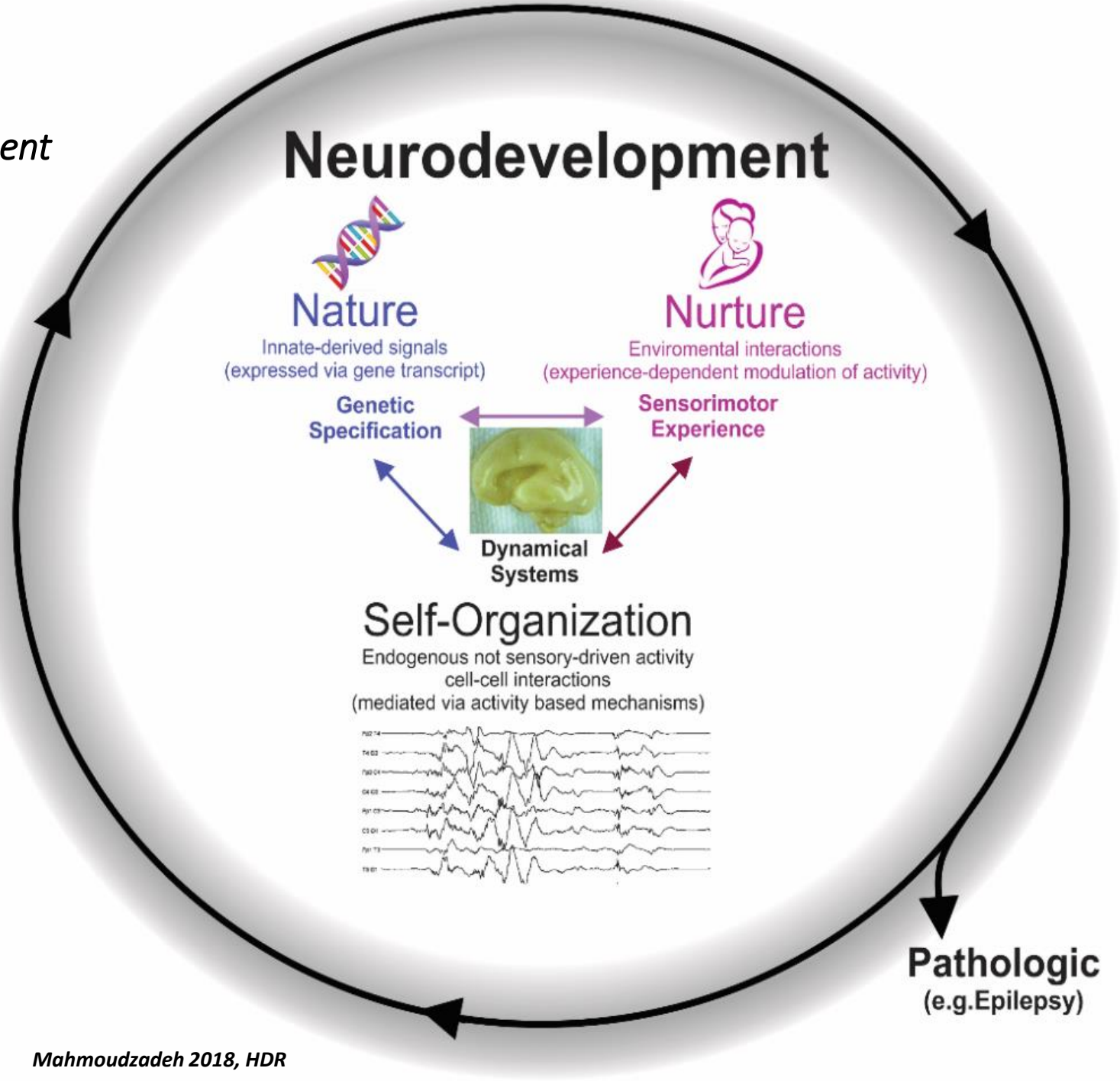


Sejnowski et al, Nature Neuroscience, 2014

Neurodevelopment

formation of neuronal networks in early development

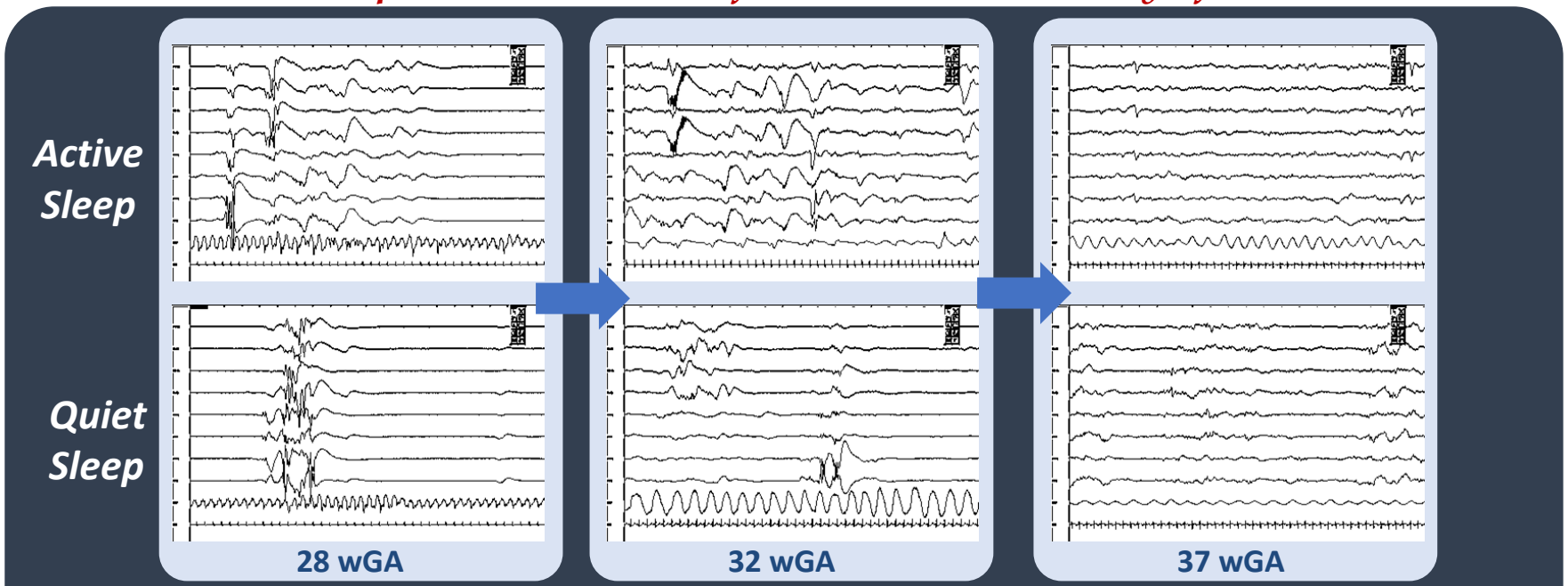
- How are these **functionality networks set up**?
- What are their abilities to **discriminate linguistic information** at this early stage of development?
- What **structures are involved**?
- Are these capabilities **specific to humans**?
- How do these networks behave in **pathological situations**?
- Can this approach be used to develop **neurobiomarkers** of normal and pathological neurodevelopment?



Mahmoudzadeh 2018, HDR

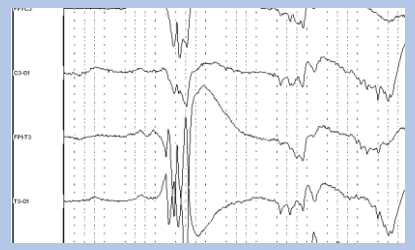
The immaturity of the cortex in 28-32 wGA premature

EEG in preterm shows the functional immaturity of the brain

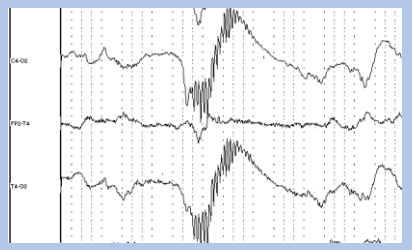


- *The discontinuity suggests that some generators are modified with the development.*
- *The occurrence of sleep stages suggests functional input from the reticular network.*

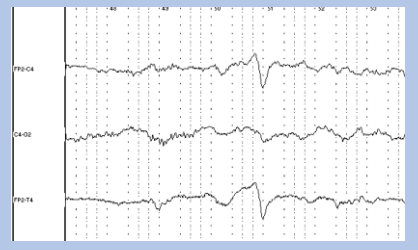
Specific features appear and disappear according to the development



Temporal theta (30w)

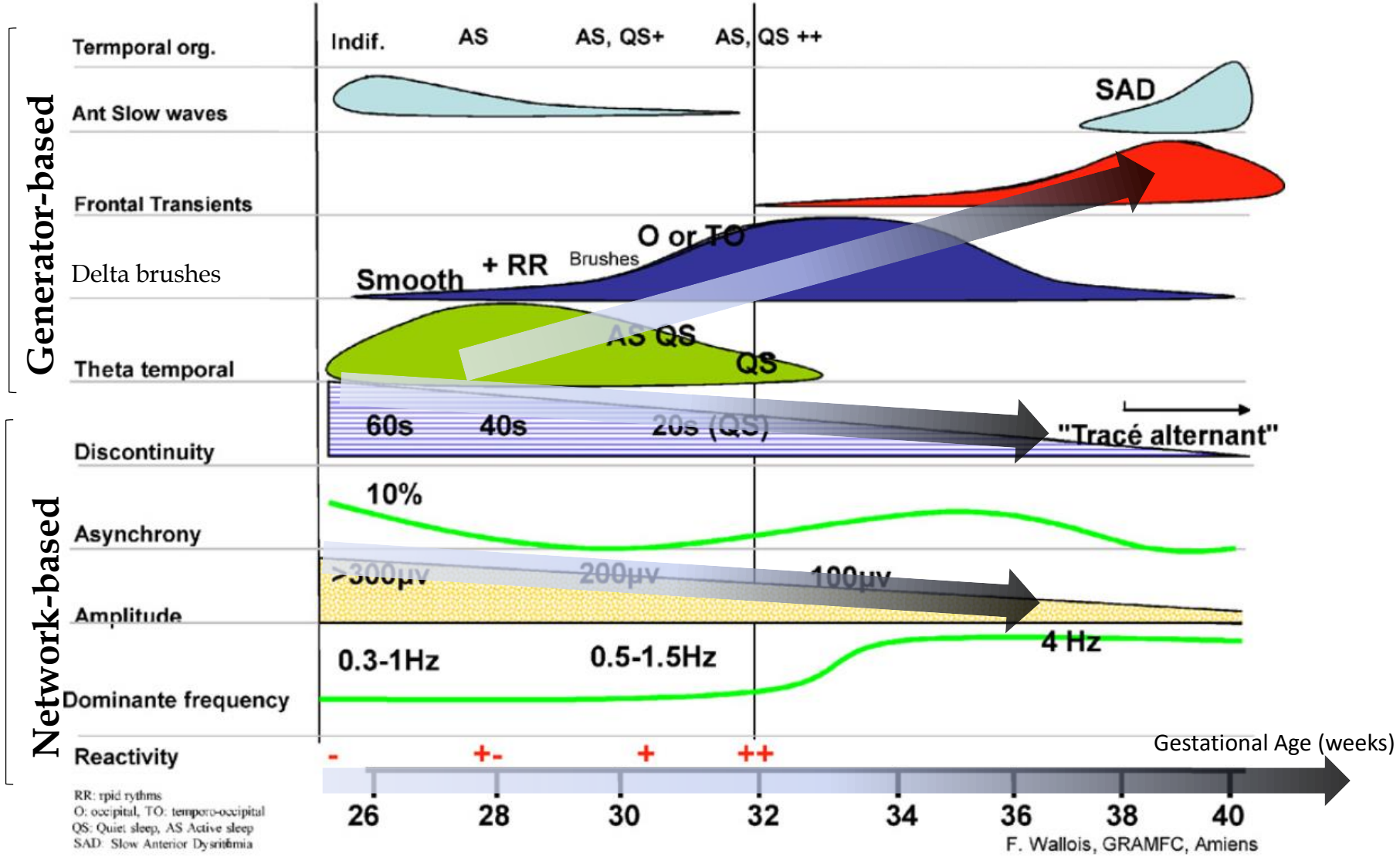


Delta Brush (32-34w)



Frontal transient (34-41w)

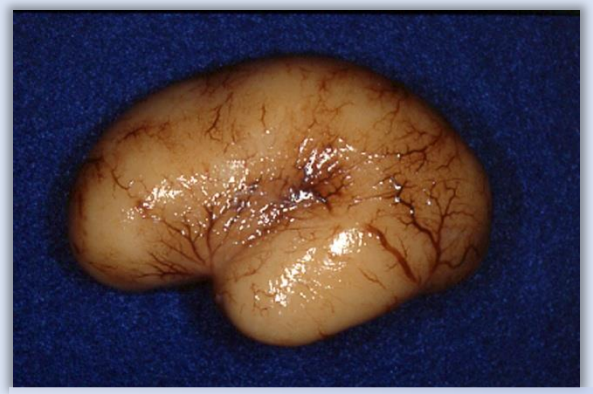
Synopsis of maturation of specific features in EEG of preterm neonates



This shows dynamic of the Brain Maturation

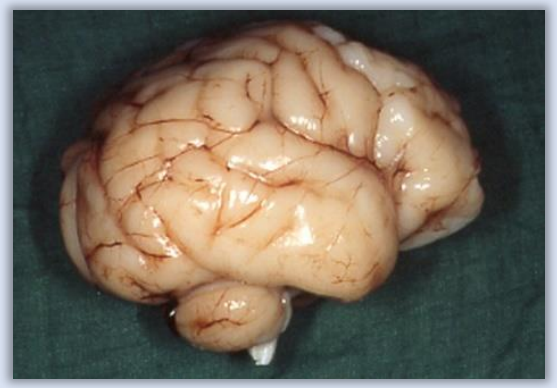
The immaturity of the cortex in 28-32 wGA premature

Brain maturation Level: **Macroscopic** Mesoscopic Microscopic

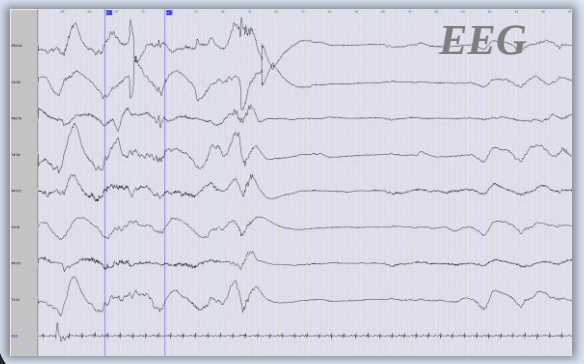


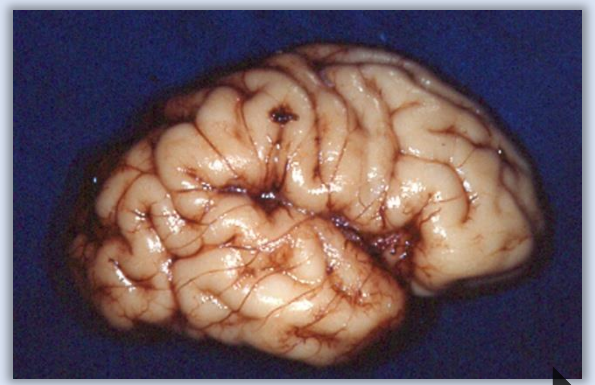
20 weeks GA

EEG



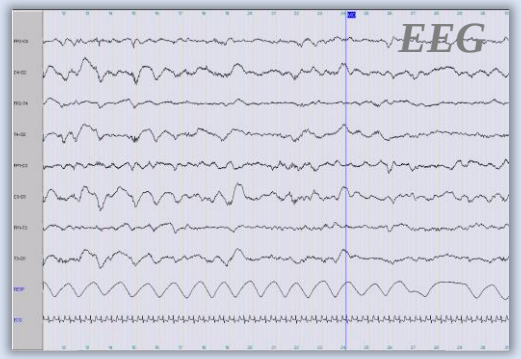
28 weeks GA





gradual gyrification

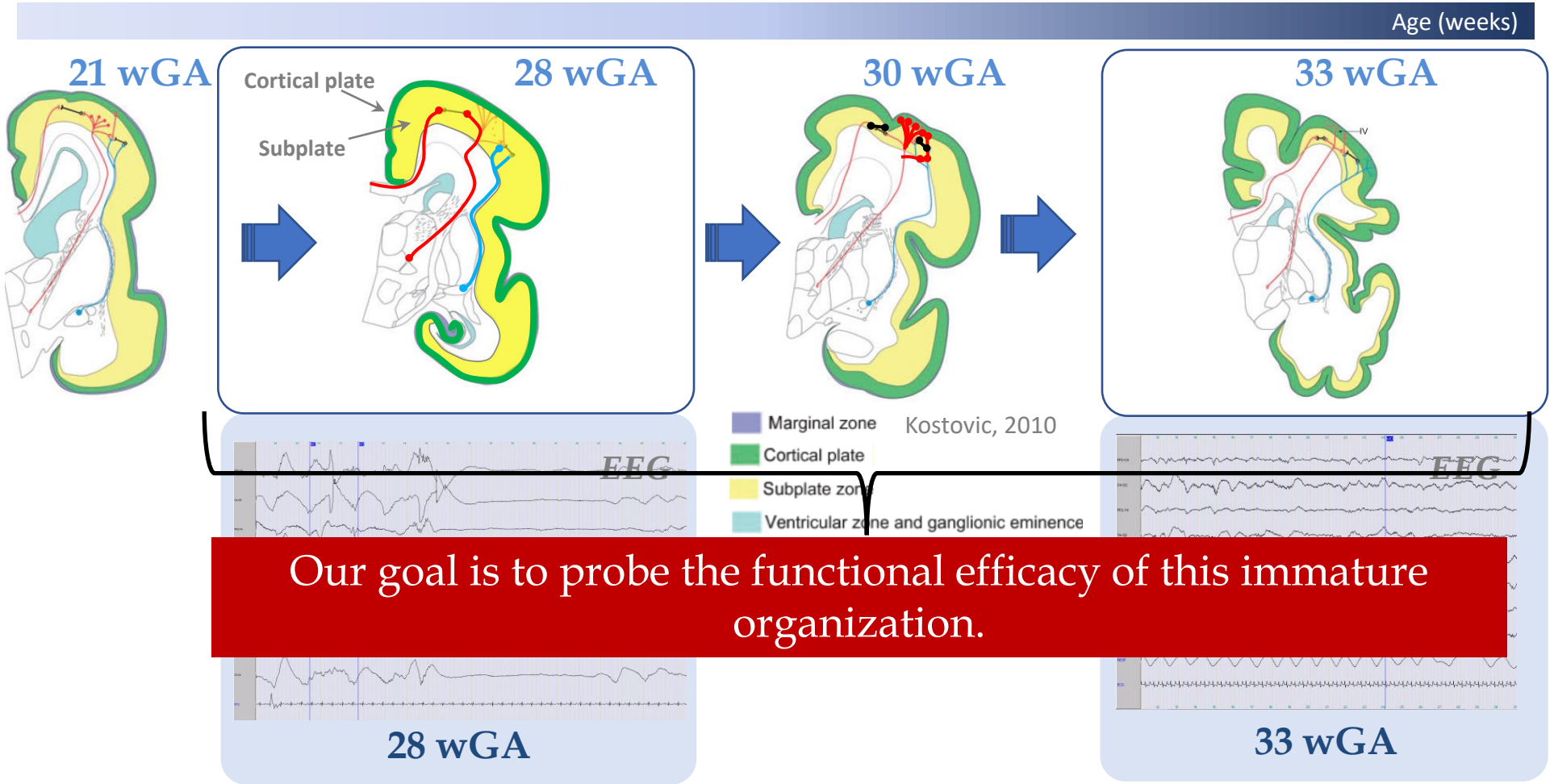
33 weeks GA



What about mesoscopic?

The immaturity of the cortex in 28-32 wGA premature

Brain maturation Level: Macroscopic **Mesoscopic** Microscopic



Our goal is to probe the functional efficacy of this immature organization.

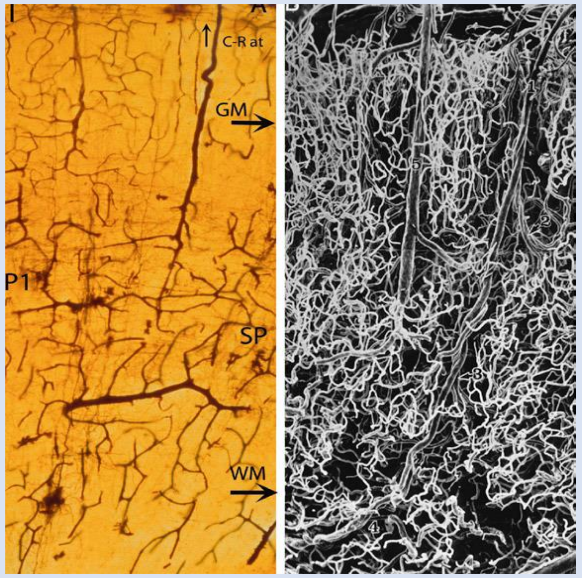
- 20-26 wGA the subplate receive thalamocortical afferents
- 26-28 wGA the first afferents reach the cortical plate
- 28-30 wGA the first synapses occur in the cortical plate

What about microscopic?

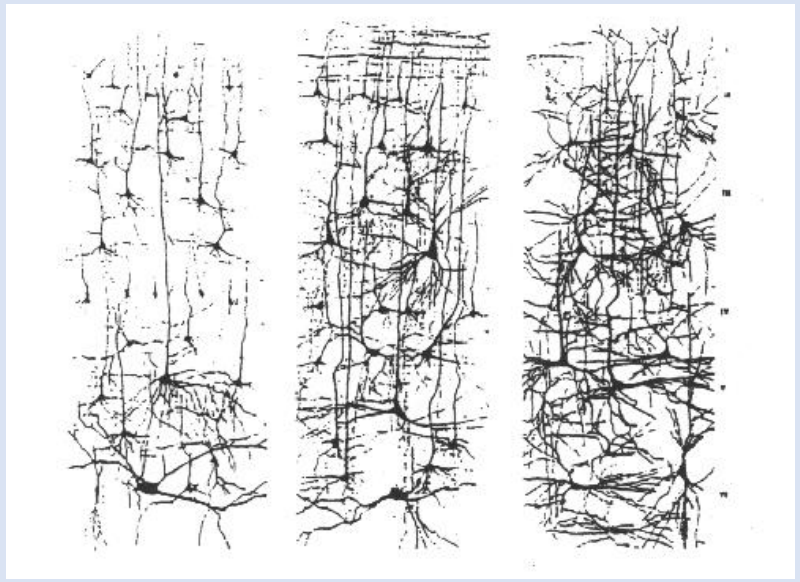
The immaturity of the cortex in 28-32 wGA premature

Brain maturation Level: Macroscopic - Mesoscopic - Microscopic

Vascular Network *interaction* **Neuronal Network**



Premature Adult



Neonate Children Adult

Marin-Padilla et al., 2011

- Both, vascular and neuronal networks in newborns are immature.
- **But the level of immaturity of each network seems well adapted**

Brain imaging methods in neonates

Structure

- Cranial Ultrasonography
- MRI
- X-ray
  - ➢ CT-scan
  - ➢ Radiography

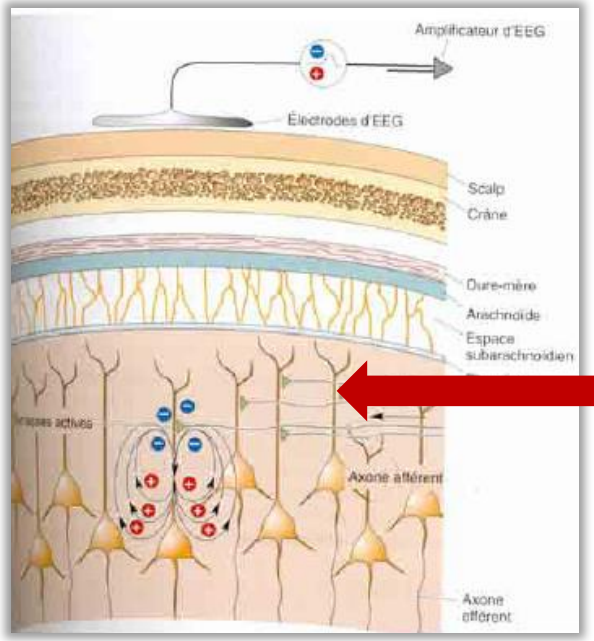
Function

- EEG
- fNIRS

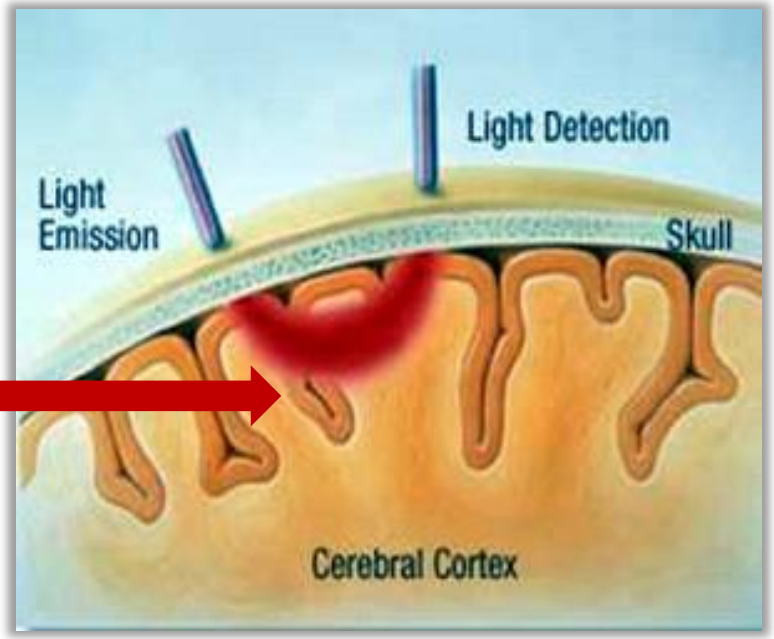
} *Preterm neonates*

- fMRI
- PET
- SPECT …

EEG: Electric (Neuronal)



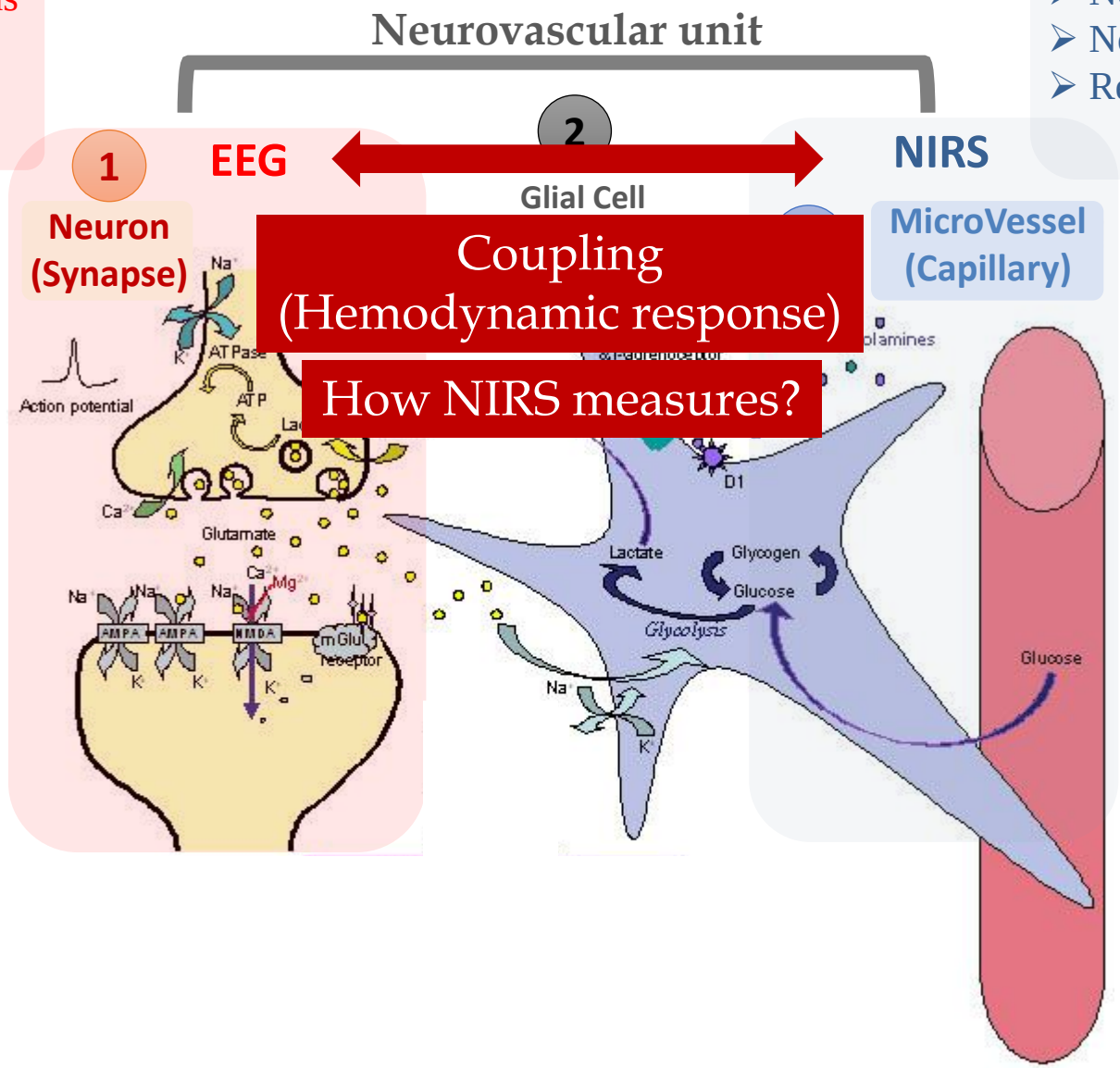
NIRS: Hemodynamic (Neurovascular)



Neurovascular coupling

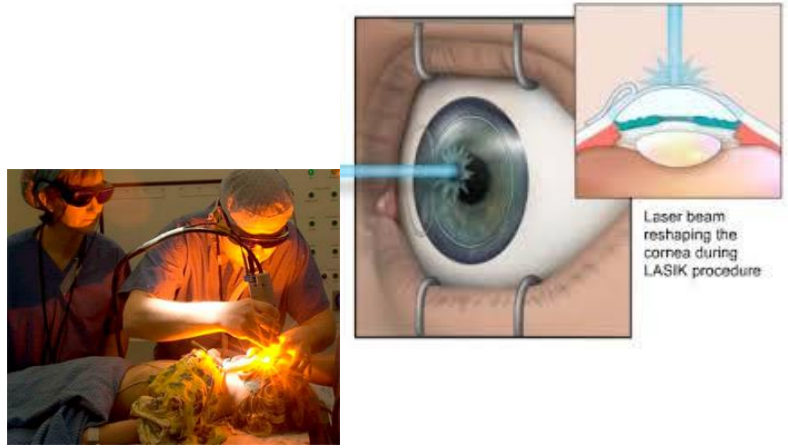
- Pyramidal neurons
- Parallel
- Synchronization
- Resolution: msec

- Neurons and Astrocytes
- No orientation
- No synchronization
- Resolution: slowNIRS: sec
  fastNIRS msec

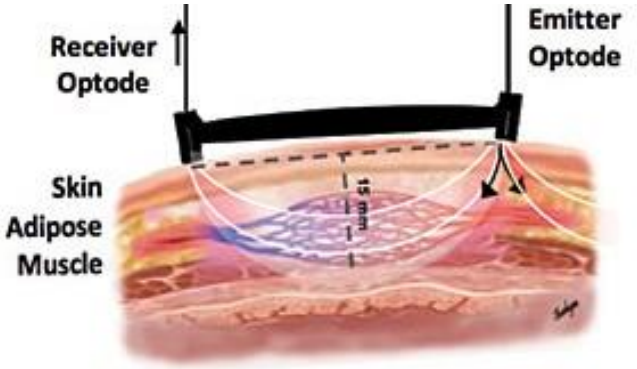


Biomedical Optics

- **Light** modifies **Tissue**
  - Laser surgery



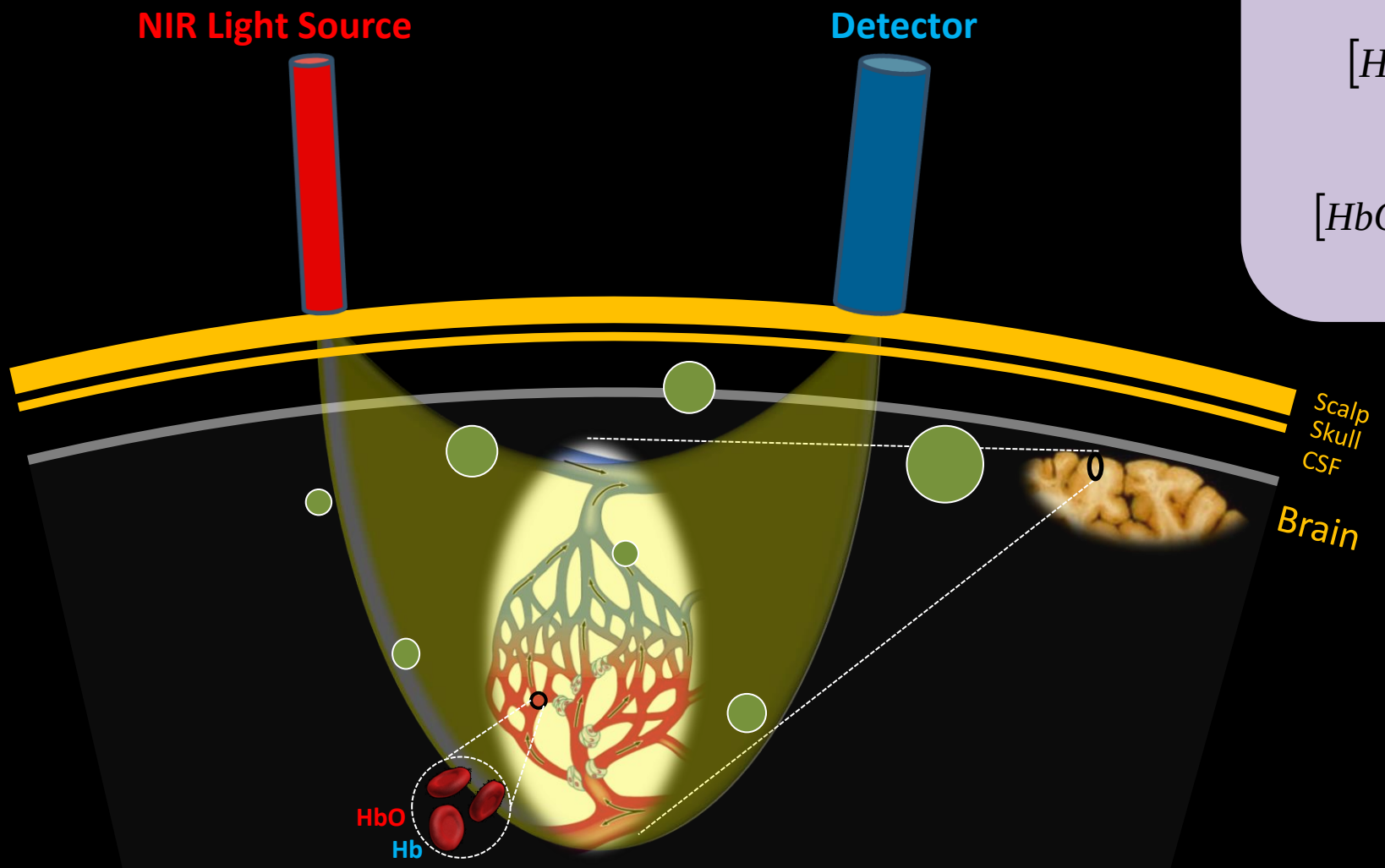
- **Tissue** modifies **Light**
  - NIR Spectroscopy



Near-Infra Red light interaction with medium

Two main process:

- Scattering
- Absorption



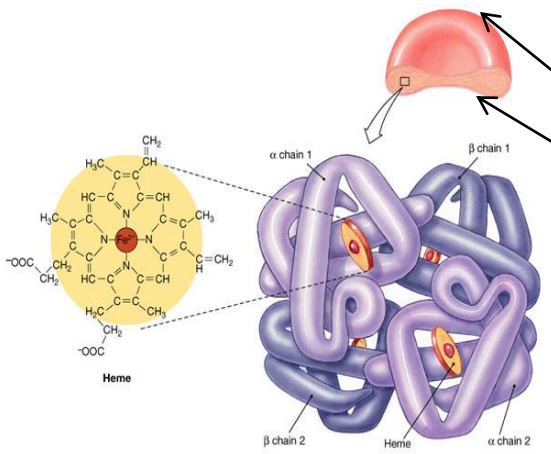
Modified Beer-Lambert Law

$$\mu_a^{\lambda} = \varepsilon_{HbO_2}^{\lambda}\left[HbO_2\right] + \varepsilon_{Hb}^{\lambda}\left[Hb\right]$$

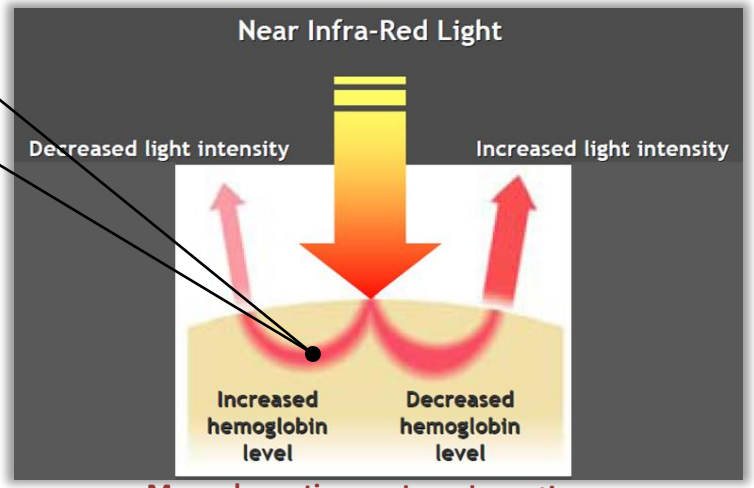
$$\left[Hb\right] = \frac{\mu_a^{\lambda_2}\varepsilon_{HbO_2}^{\lambda_1} - \mu_a^{\lambda_1}\varepsilon_{HbO_2}^{\lambda_2}}{\varepsilon_{HbO_2}^{\lambda_1}\varepsilon_{Hb}^{\lambda_2} - \varepsilon_{HbO_2}^{\lambda_2}\varepsilon_{Hb}^{\lambda_1}}$$

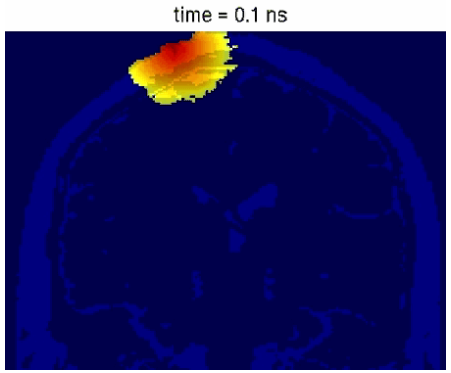
$$\left[HbO_2\right] = \frac{\mu_a^{\lambda_1}\varepsilon_{Hb}^{\lambda_2} - \mu_a^{\lambda_2}\varepsilon_{Hb}^{\lambda_1}}{\varepsilon_{HbO_2}^{\lambda_1}\varepsilon_{Hb}^{\lambda_2} - \varepsilon_{HbO_2}^{\lambda_2}\varepsilon_{Hb}^{\lambda_1}}$$

Absorption characteristics of hemoglobin



Hemoglobin molecule





Modified Beer-Lambert Law

$$\mu_a^{\lambda} = \varepsilon_{HbO_2}^{\lambda}[HbO_2] + \varepsilon_{Hb}^{\lambda}[Hb]$$

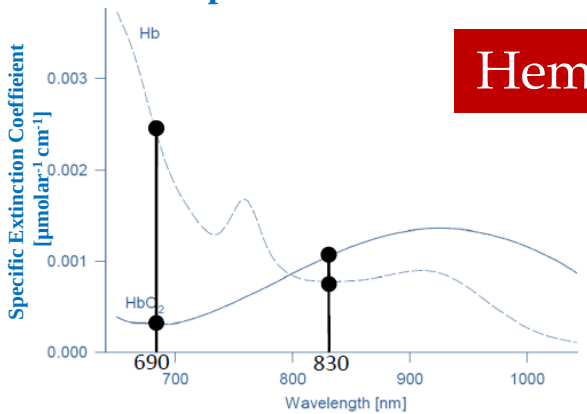
Hemoglobin

$$[Hb] = \frac{\mu_a^{\lambda_2}\varepsilon_{HbO_2}^{\lambda_1} - \mu_a^{\lambda_1}\varepsilon_{HbO_2}^{\lambda_2}}{\varepsilon_{HbO_2}^{\lambda_1}\varepsilon_{Hb}^{\lambda_2} - \varepsilon_{HbO_2}^{\lambda_2}\varepsilon_{Hb}^{\lambda_1}}$$

Oxy-Hemoglobin

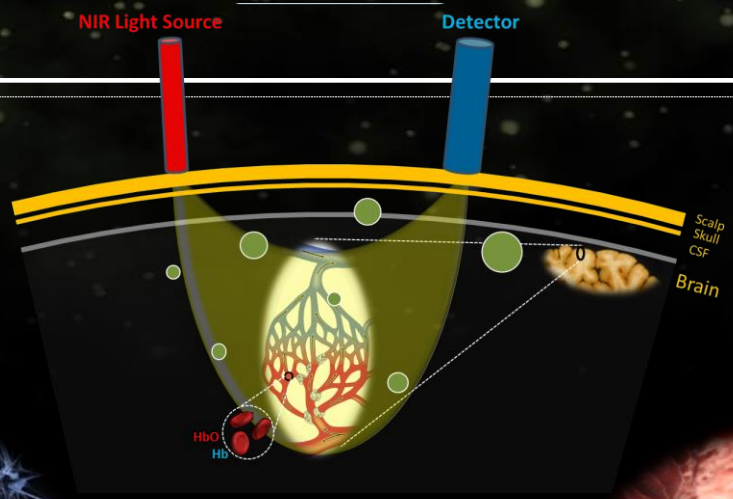
$$[HbO_2] = \frac{\mu_a^{\lambda_1}\varepsilon_{Hb}^{\lambda_2} - \mu_a^{\lambda_2}\varepsilon_{Hb}^{\lambda_1}}{\varepsilon_{HbO_2}^{\lambda_1}\varepsilon_{Hb}^{\lambda_2} - \varepsilon_{HbO_2}^{\lambda_2}\varepsilon_{Hb}^{\lambda_1}}$$

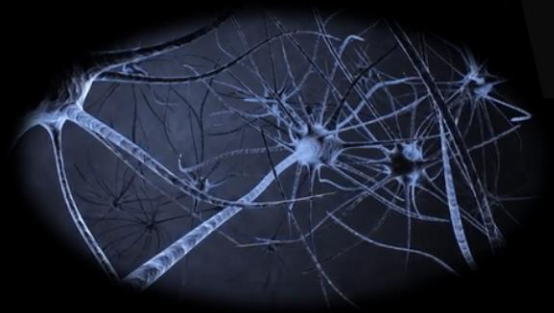
Optical window

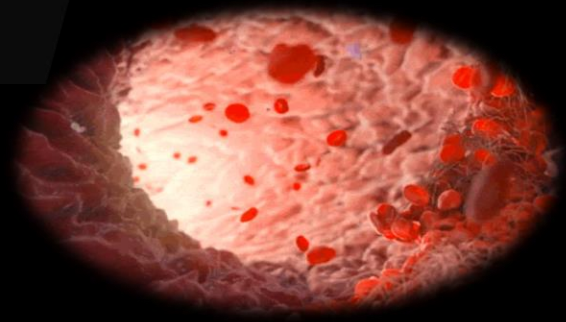


Hemodynamic Response?

Optical signal (Slow *vs.* Fast)







Fast optical signal (FOS, EROs)

changes in scattered light (Neural Activity)

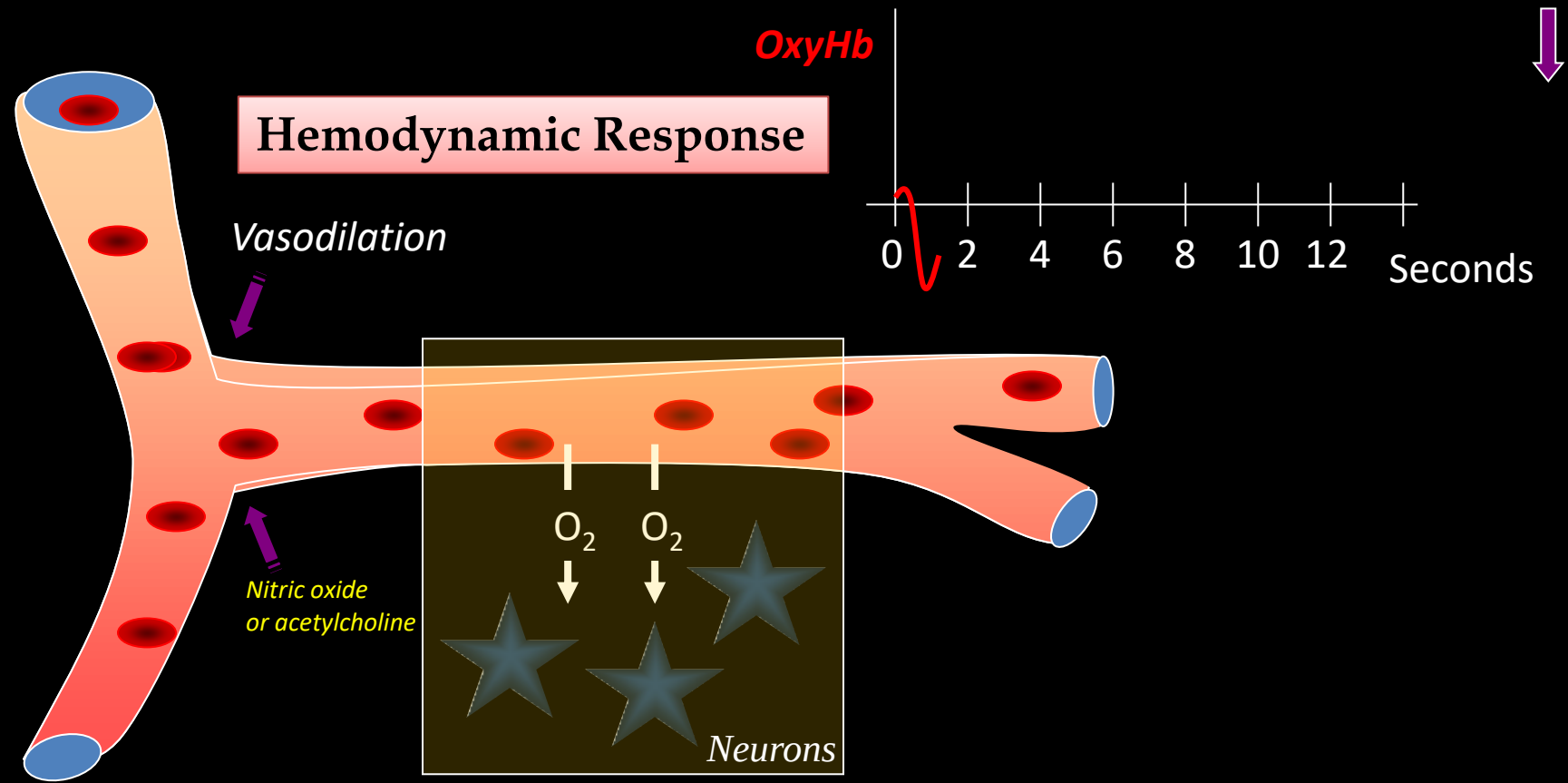
fast effects (with a 50–500-ms latency)

Slow optical signal

changes in light absorption (Hemodynamic Activity) oxy/deoxyhemoglobin concentration

slow effects (with a 2–10-s latency).

Hemodynamic Response



Neurons consume energy (glucose) when activated

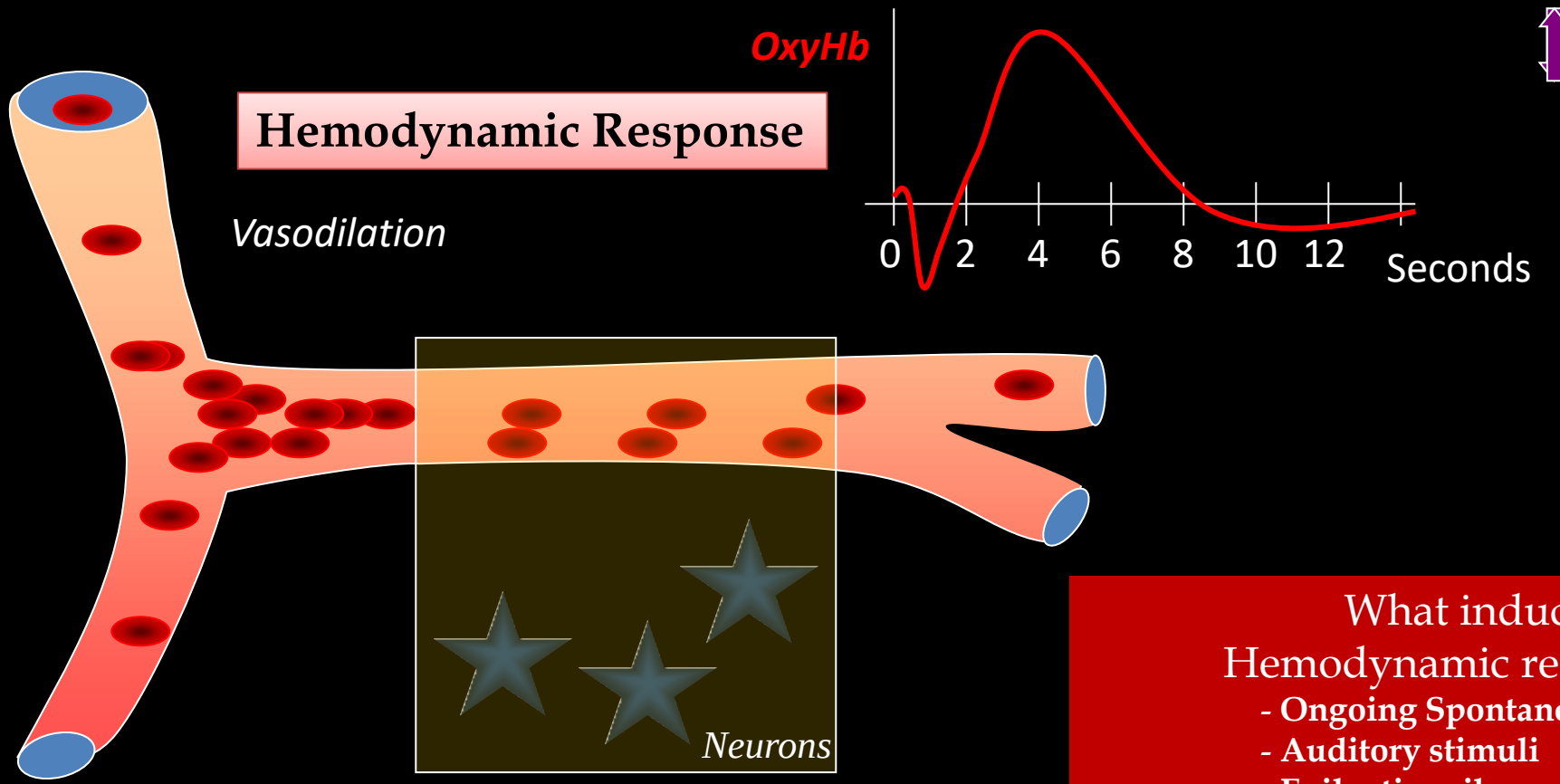
Oxygen is required to metabolize the glucose

As clusters of neurons are activated, there is an increased need for oxygen in that area

Oxygen is transported to neural tissue via oxy-hemoglobin in the blood

The oxygen exchange occurs in the capillary beds

Hemodynamic Response



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Oxygen is required to metabolize the glucose

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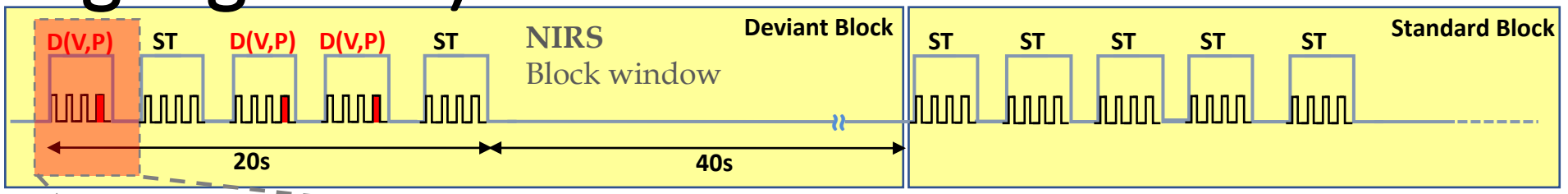
The oxygen exchange occurs in the capillary beds

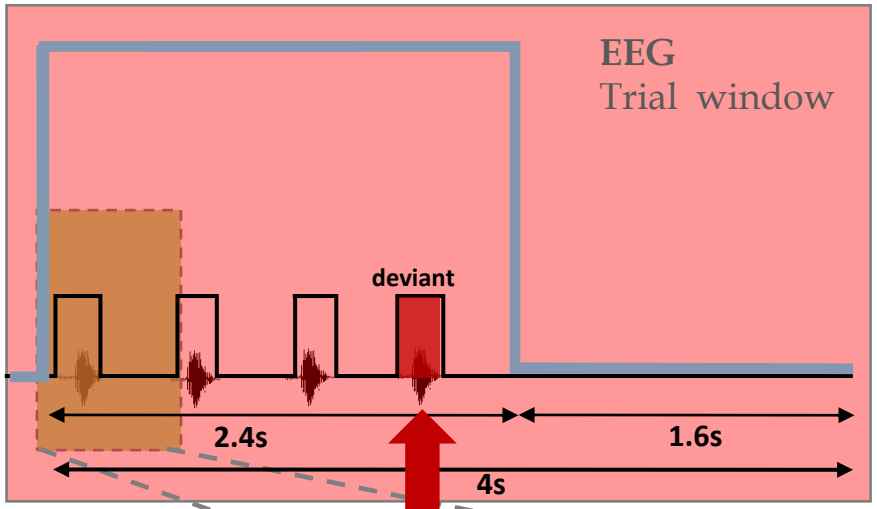
What induce Hemodynamic response?

- **Ongoing Spontaneous activities**
- **Auditory stimuli**
- **Epileptic spikes**
- **…**

Preterm (Language task)



A



B

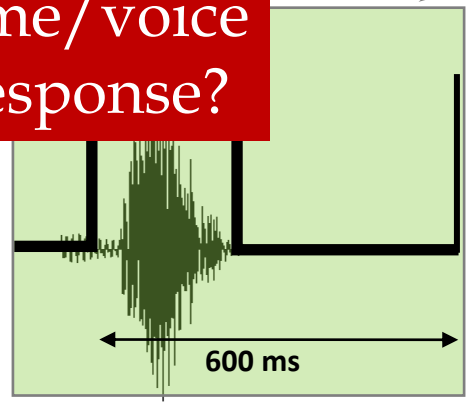
ST : Standard trial

D(V,P): Deviant (Voice,Phoneme) trial

Experimental Design

- Duration: **108 blocks**
- Auditory stimulation: **20 sec**
- Silence: **40 sec**
- Phoneme change: **ba/ga**
- Voice change: **male / female**

Is changes of phoneme/voice induced electrical response?



C

ERP (Event related potential)

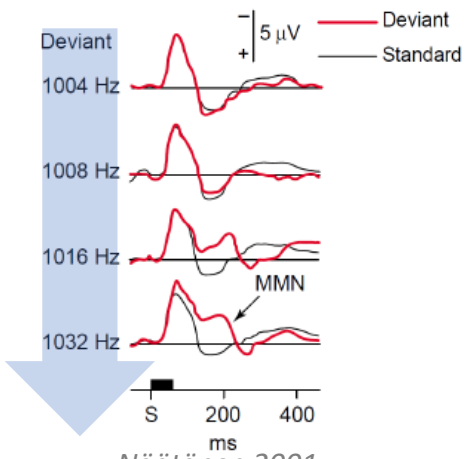
Mismatch negativity (MMN)

- The mismatch negativity (MMN) is a component of the event-related potential (ERP) to an odd stimulus in a sequence of stimuli.

- MMN is largest in the **frontal** and **central** location of electrodes.

Adults

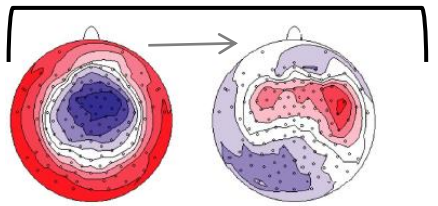
Frequency change



Näätänen 2001

Phoneme change (/ra/ , /la/)

MMN



MMN 1: ~200n 134-264 ms

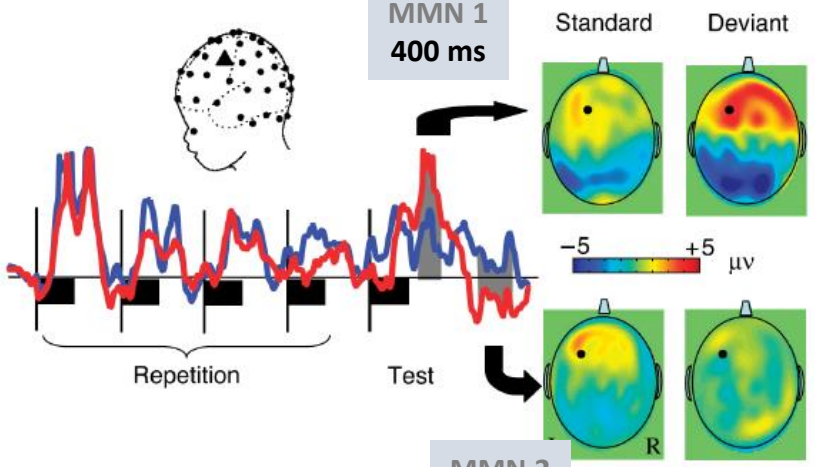
MMN 2: ~357ms 330-384 ms

Zevin, 2010

Infant

3 months old

Phoneme change (/ba/, /ga/)



MMN 1
400 ms

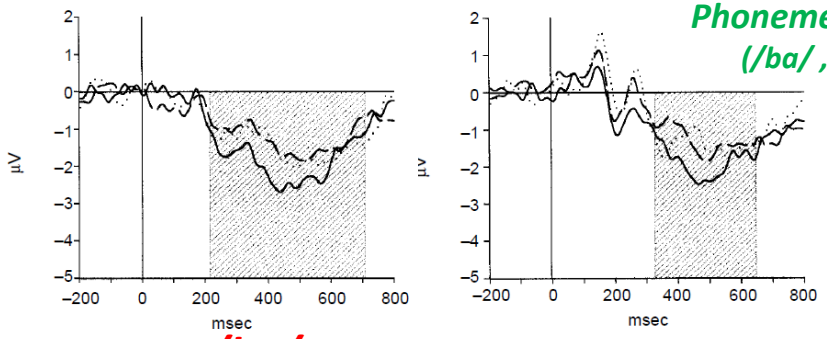
MMN 2
600 ms

Dehaene-Lambertz, 2004

Children

5-10 years

Phoneme change (/ba/ , /ga/)



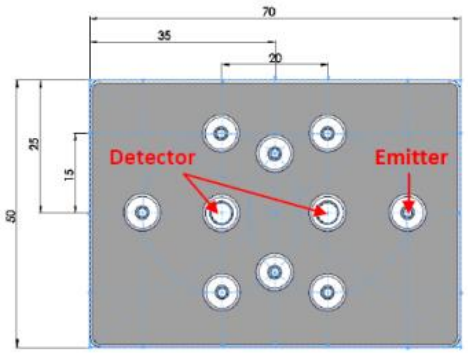
MMN
218-706 ms

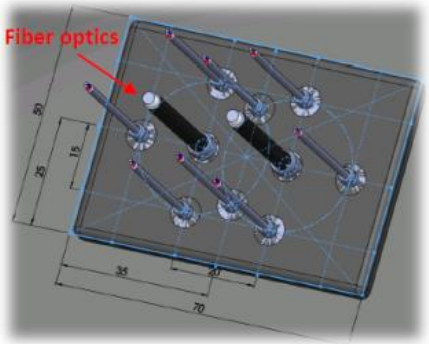
MMN
339-656 ms

Uwer, 2002

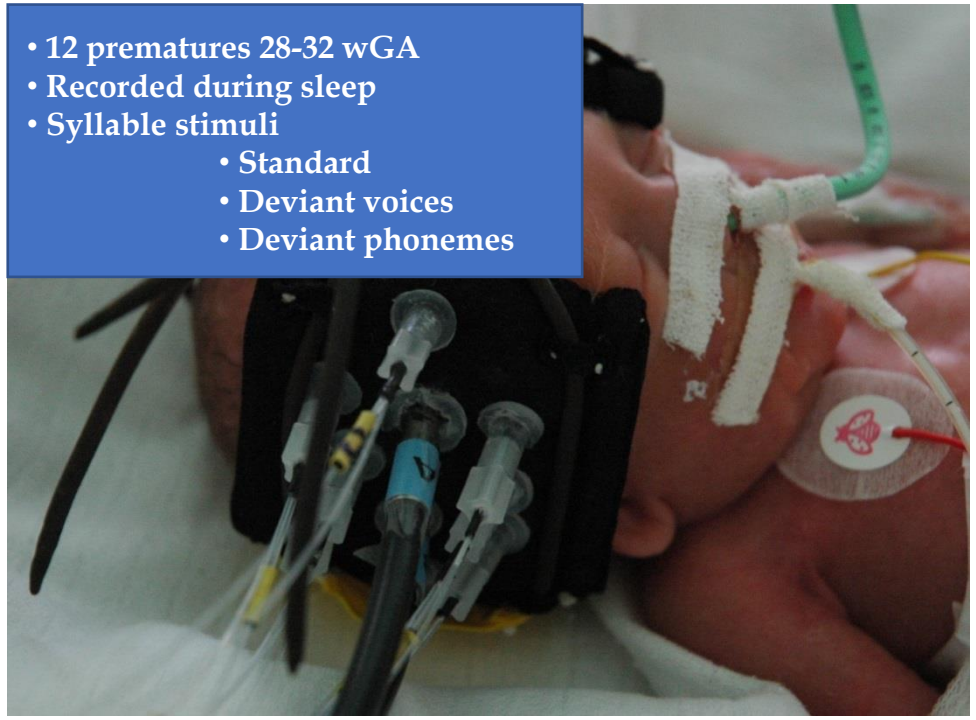
Optical probe

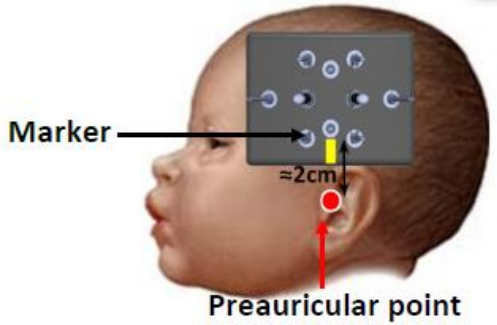
- A probe, especially designed to fit comfortably to preterm head.
- 16 emitters (8 : each hemisphere)
- 4 detectors (2 : each hemisphere)
- It covers perisylvian areas

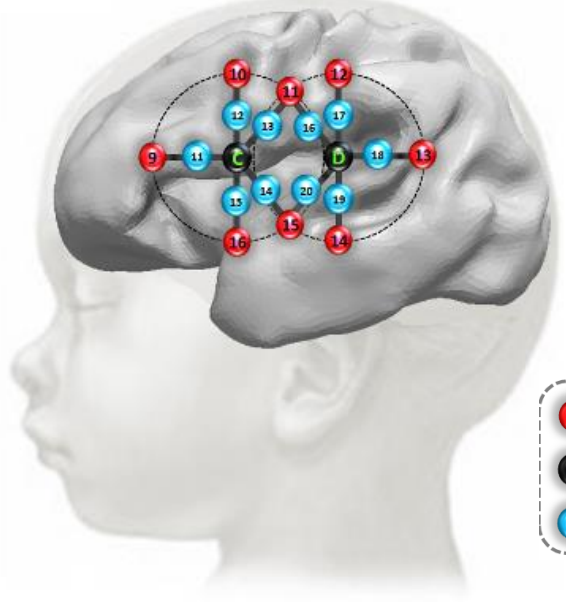




- 12 prematures 28-32 wGA
- Recorded during sleep
- Syllable stimuli
  - Standard
  - Deviant voices
  - Deviant phonemes

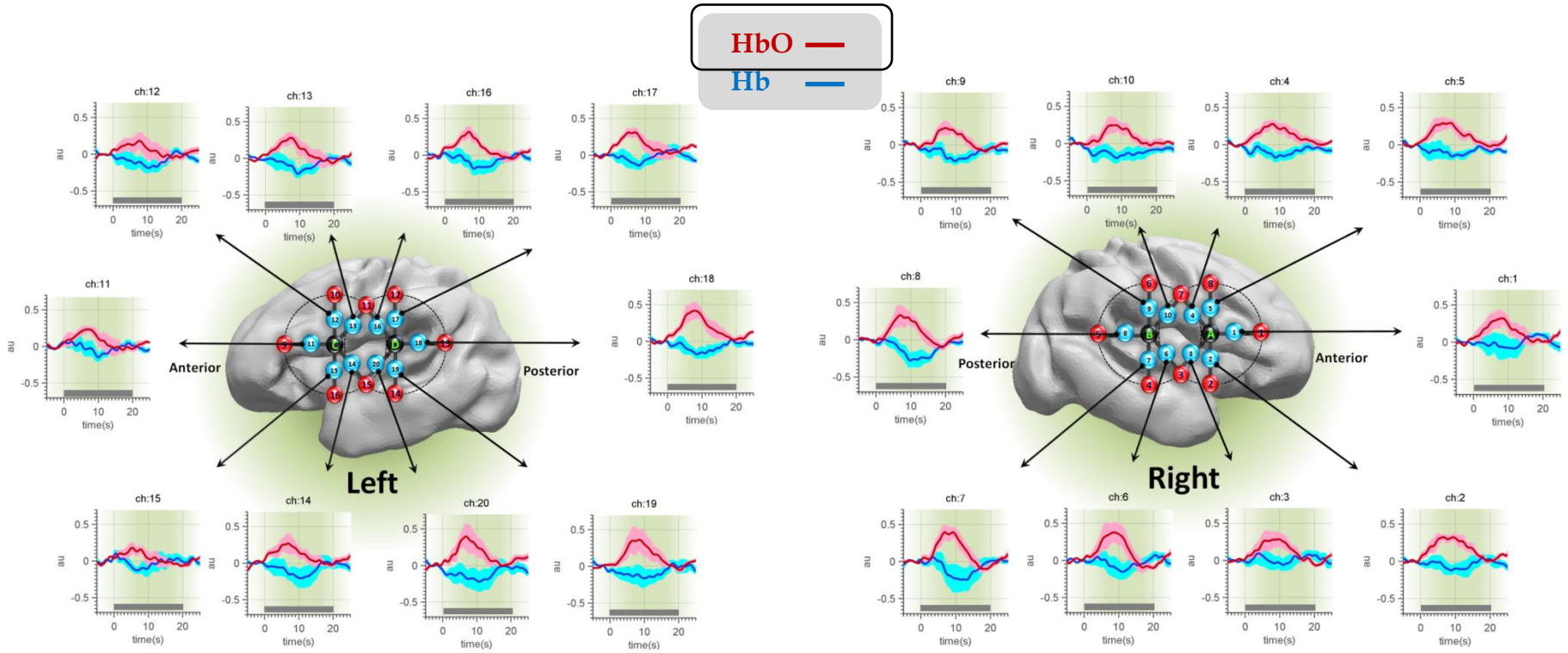






Auditory hemodynamic Response

Typical Hemodynamic responses across all conditions (ST+DV+DP)

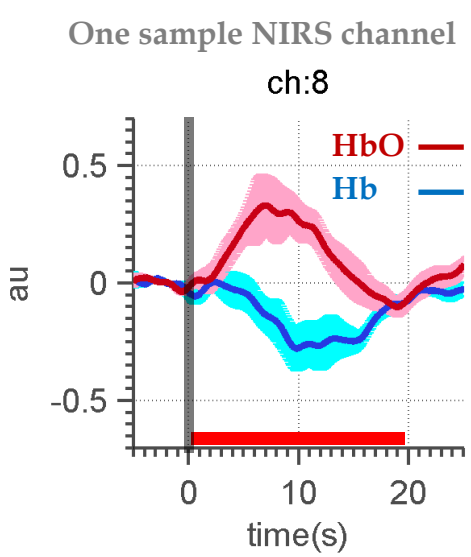


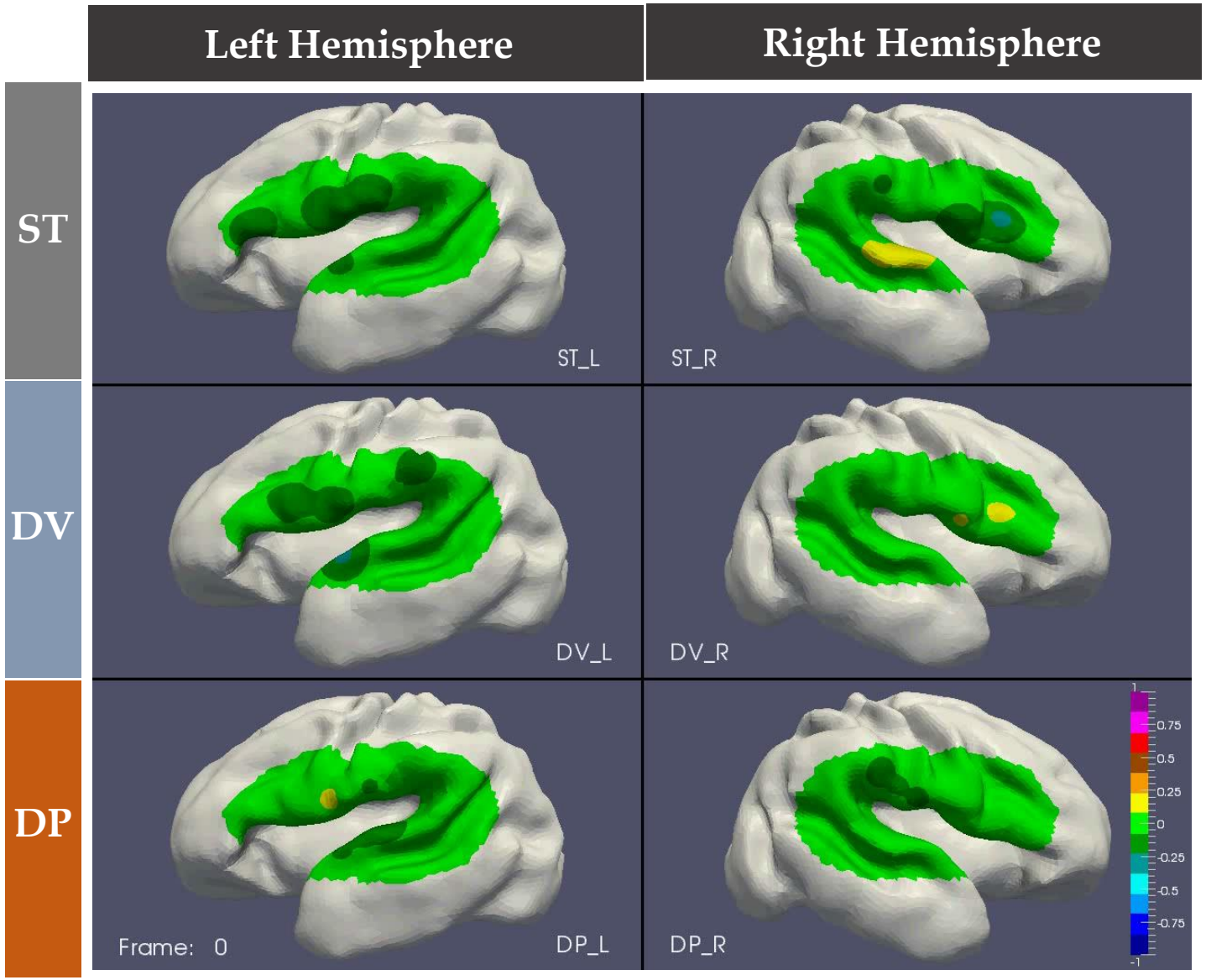
Speech stimuli induced typical neurovascular coupling with marked activation in perisylvian areas notably in the posterior part of the *planume*.

This confirms the maturity of neurovascular coupling

Video: [HbO]

Dynamic of language processing



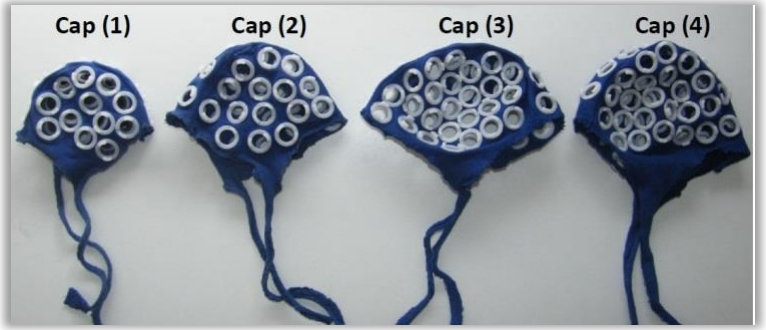


Stim onset: Frame 47

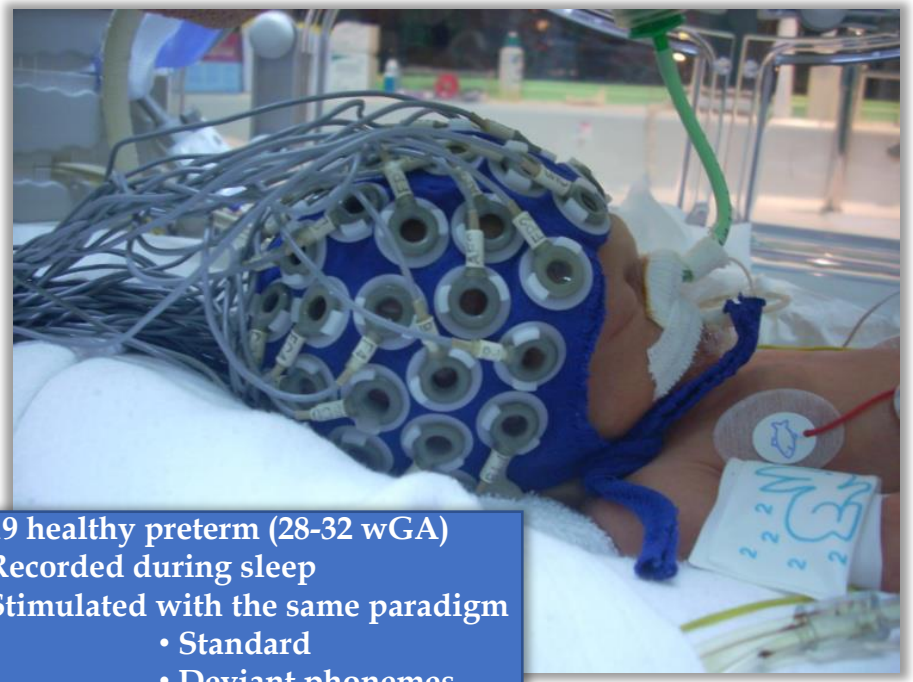
High-Resolution EEG

Event Related Potential (ERP)

Different caps for preterm HR-EEG recording



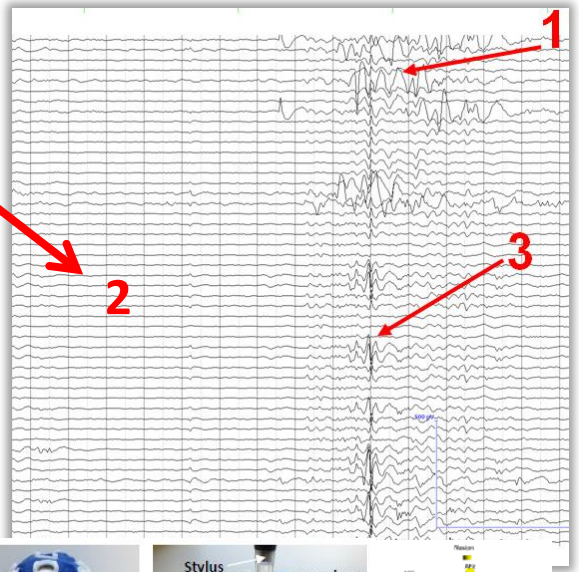
	ERP (µV)	EEG (µV)	Actual SNR	Desired SNR	# Trial
2	2	5	0.400	2	25
	2	10	0.200	2	100
	2	20	0.100	2	400
	2	30	0.067	2	900
	2	40	0.050	2	1,600
	2	50	0.040	2	2,500
1 or 3	2	100	0.020	2	10,000
	2	150	0.013	2	22,500
	2	200	0.010	2	40,000
	2	250	0.008	2	62,500
	2	300	0.007	2	90,000

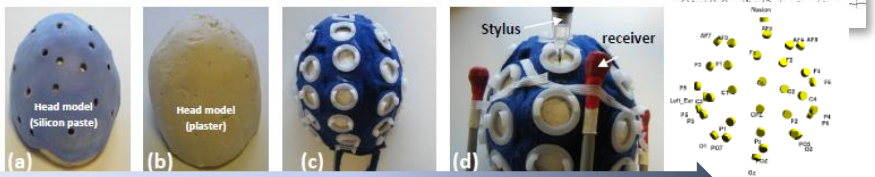


- 19 healthy preterm (28-32 wGA)
- Recorded during sleep
- Stimulated with the same paradigm
  - Standard
  - Deviant phonemes
  - Deviant voices

Neonatal EEG

trial selection: during discontinuity periods



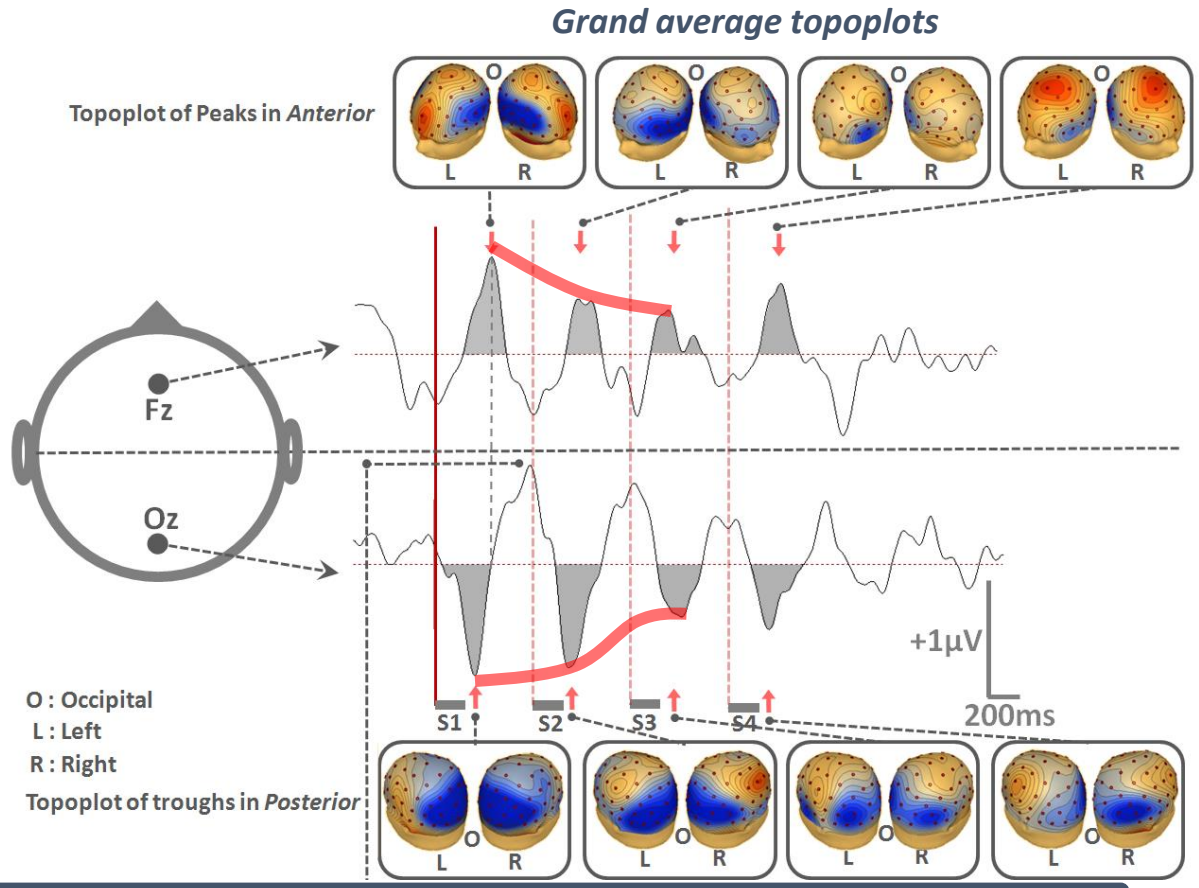


Reconstruction of 3D electrode position

Auditory Event-Related Potential

As early as 28-32wGA,
neuronal networks can already **synchronize** and thus produce ERPs.

- Each syllable induces an ERP with
  - Frontal positivity
  - Posterior negativity
- Habituation

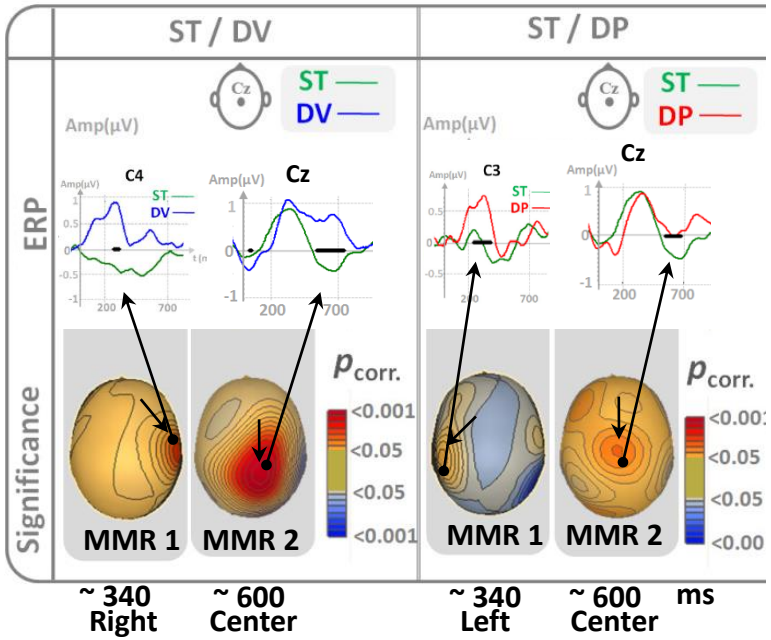


Habituation is already present,
which is a prerequisite for mismatch responses and thus discrimination.

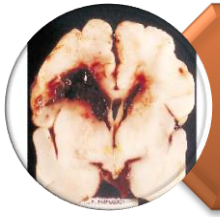
Mismatch Response

- Change of voice (DV)
  - MMR 1: Right temporal
  - MMR 2: Central
- Change of phoneme (DP)
  - MMR 1: Left temporal
  - MMR 2: Central
- Deviant voices and phonemes induced different Mismatch responses revealing that voice and phonemes can be coded in premature neonates by different neuronal networks.

Preterm

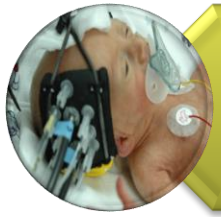


Born prematurely



Intra-Ventricular Hemorrhage (IVH):
risk factor for cognitive impairment

Children with delays in language and speech



Detecting this inability as early as possible in the first months of life
[using functional imaging: EEG-NIRS]

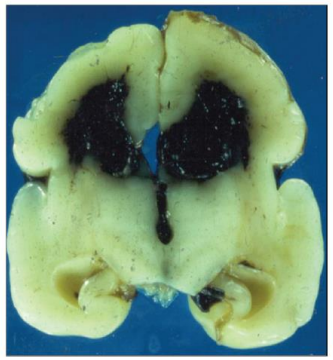
To treat more efficiently
these disorders

Neonatal IntraVentricular Hemorrhage (IVH)

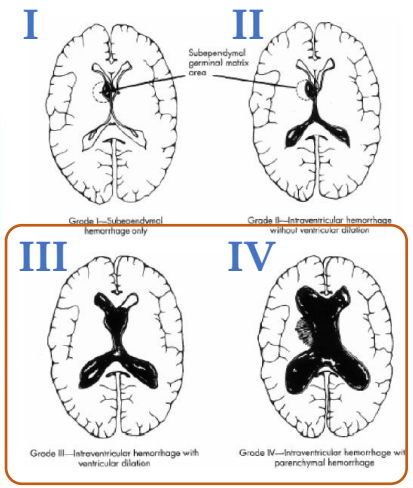
IVH:
- The most frequent intracranial hemorrhage in the neonatal period
- It is observed almost exclusively as a result of prematurity.

- Preterm neonates are at high-risk of IVH because of their lack of ability to regulate Cerebral Blood Flow (CBF) and Cerebral Blood Pressure (CBP).

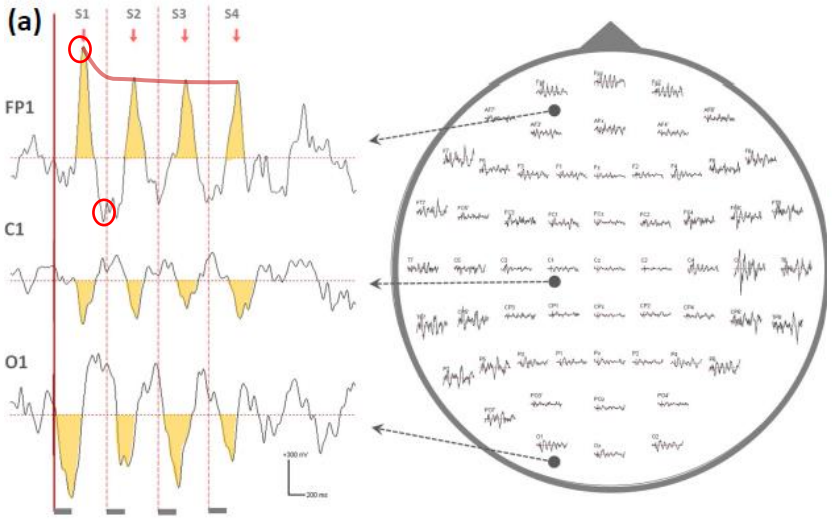
- Preterms (28-32 wGA) with IVH
  - EEG: 8 neonates
  - NIRS: 7 neonates



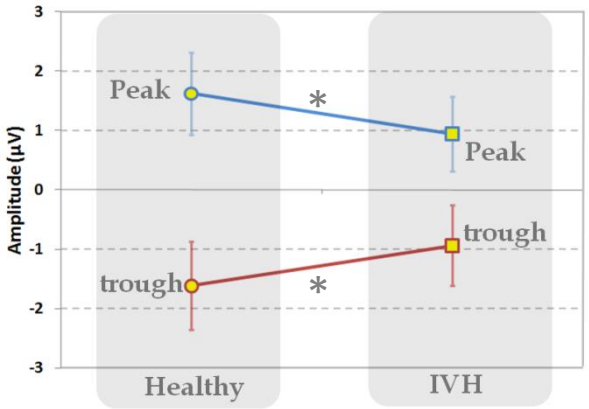
Grade I-IV



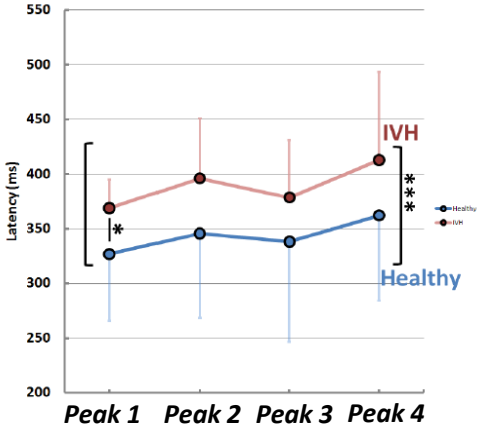
Evoked Related Potentials in IVH



Amplitude



Peak Latency

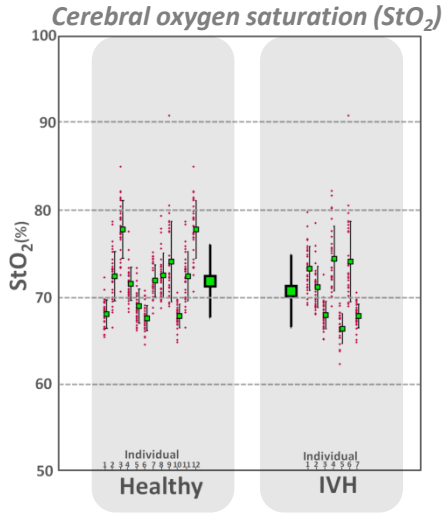


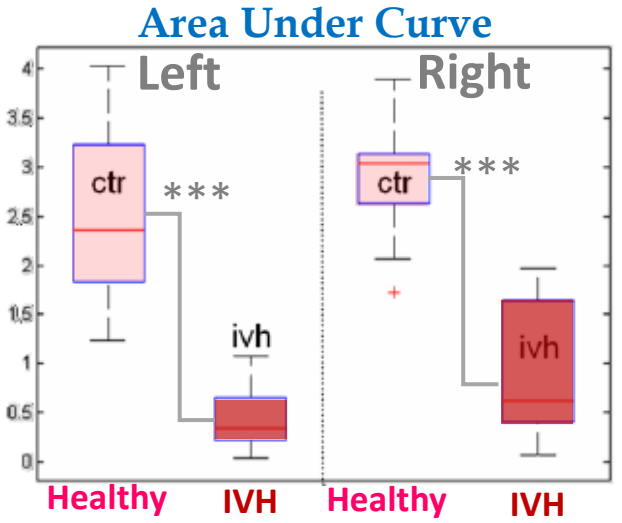
*P<0.05
***P<0.001

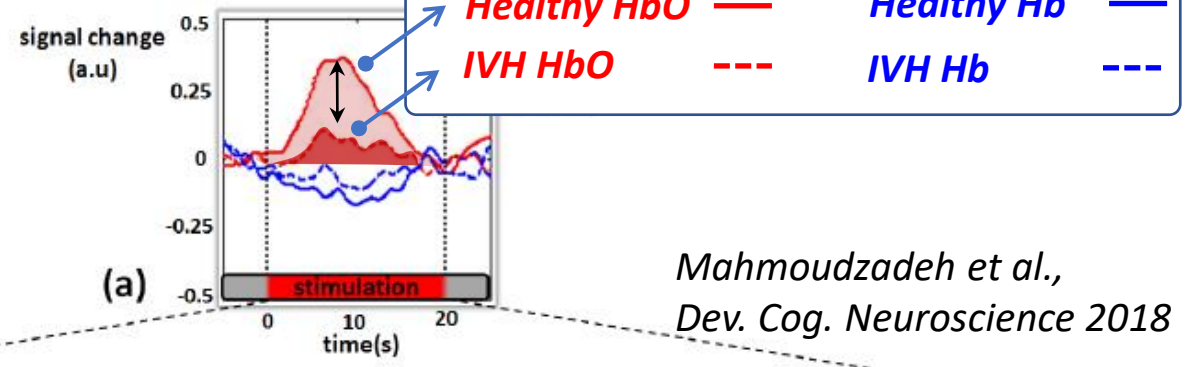
Clinical impact

- StO_2 is similar in both groups :
  - it is unlikely that **cerebral hypoxia** would be the cause of impairment of a neurovascular coupling.

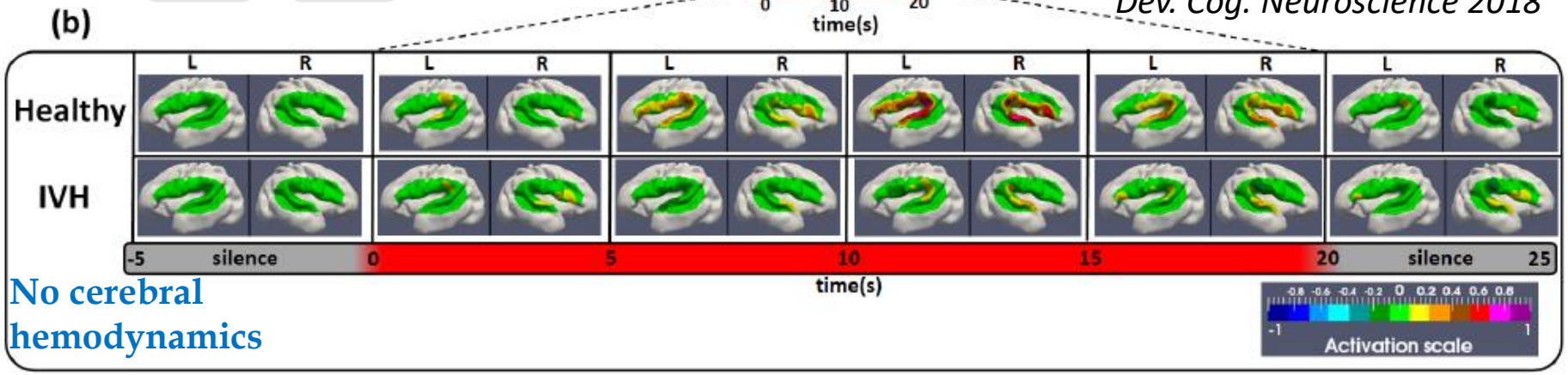
No Sto2 difference







Mahmoudzadeh et al., Dev. Cog. Neuroscience 2018



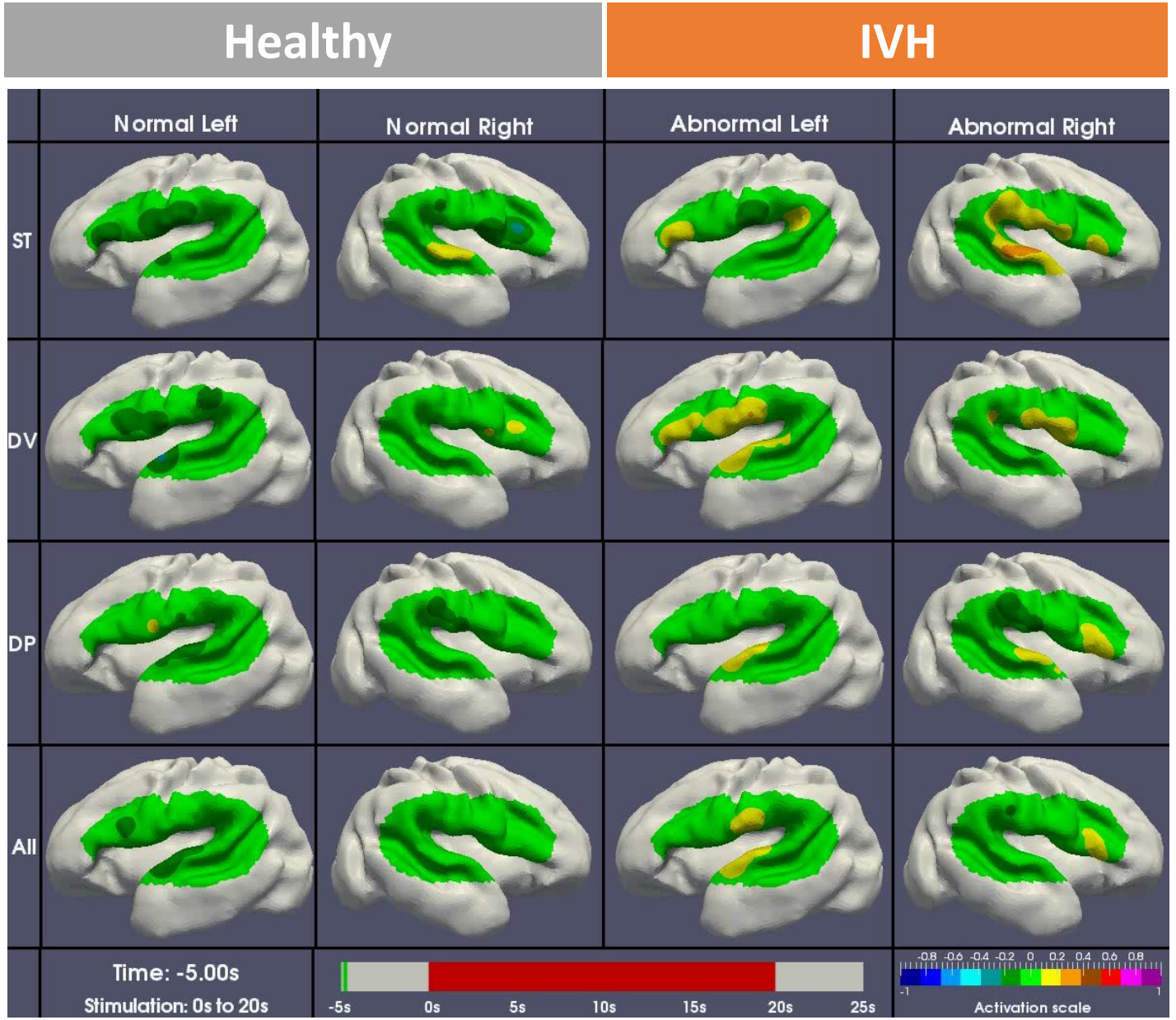
No cerebral hemodynamics

Impaired Neurovascular Coupling

Clinical application of NIRS

Comparison between Healthy and IVH

Video: [HbO]



Questions?