Implantable ultrasound device for repeated opening of the blood brain barrier: A promising technology for drug delivery into the brain

C. Lafon [1], M. Canney [12], K. Beccaria [2], C. Horodyckid [2], A. Vignot [2], J.Y. Chapelon [1], A. Carpentier [2]

1- LabTau, INSERM, University of Lyon, Lyon, France

2 – Carthera SAS, Paris, France

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Brain tumors = a dramatic prognosis

- Why ? The blood-brain barrier (BBB) limits the efficacy of chemotherapy
- US demonstrated to induced BBB opening in pre-clinical studies using pulsed ultrasound + US contrast agents
  - Skull is main problem for clinical application
  - MRguided Extracorporeal US Phased Arrays (McDannold et al. 2012, Cancer Research, …)
  - Heavy method for routine repeated BBB opening at each chemotherapy session

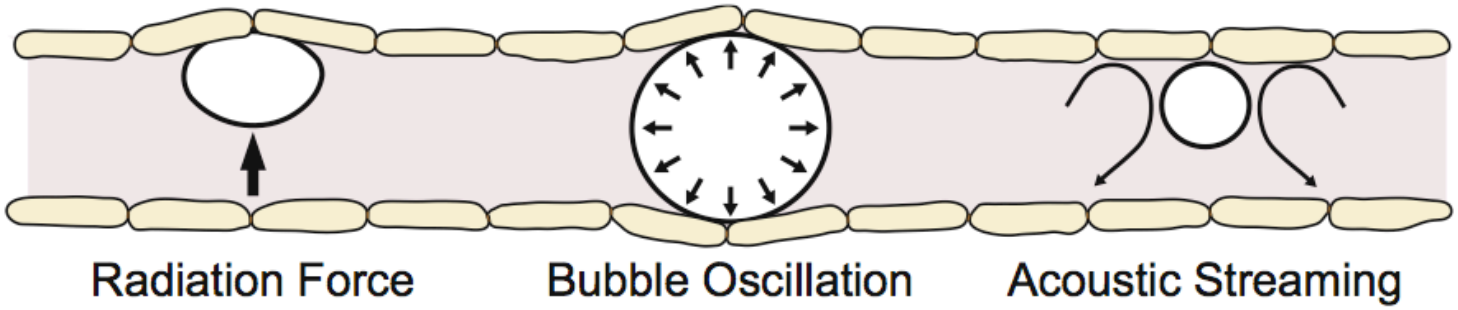
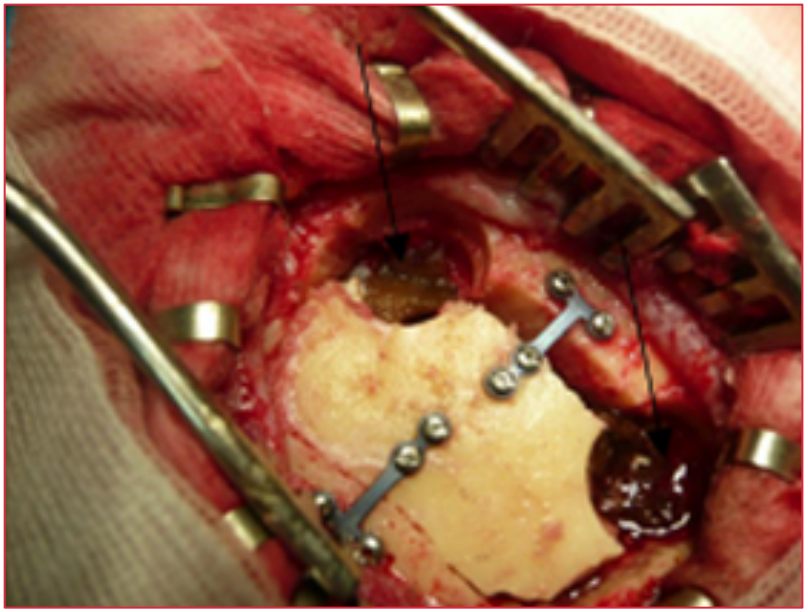


Figure from Vykhodtseva et al. (2008)

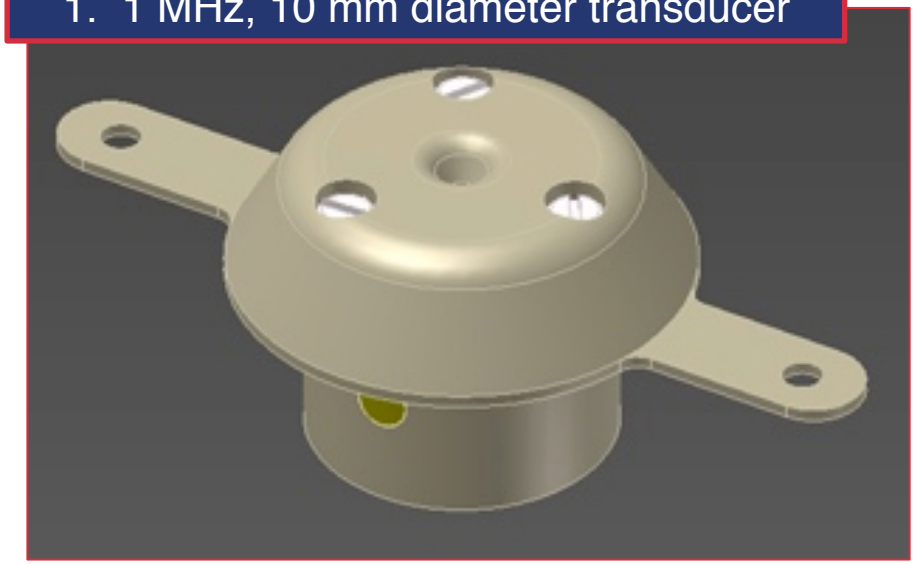
Original concept

Use skull burr hole (1-cm) after tumor resection for an implantable ultrasound device to achieve simple, repeated BBB openings

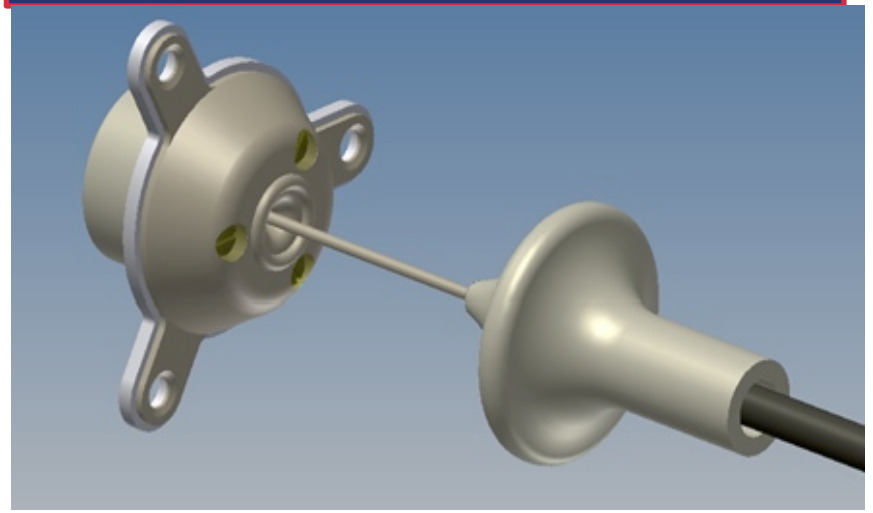


Implantable US Device: Concept

1. 1 MHz, 10 mm diameter transducer



2. Transdermal needle connection

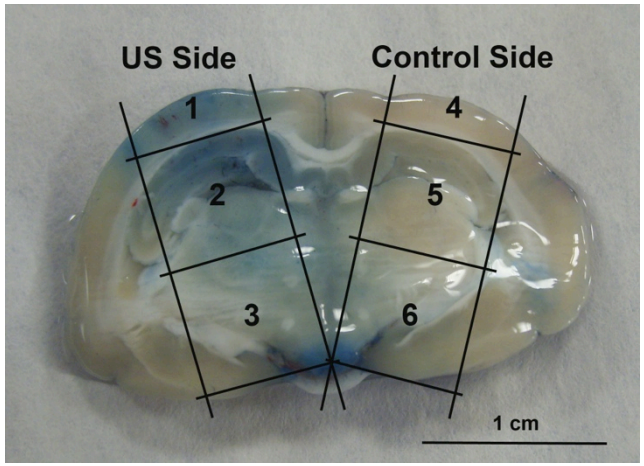


3. External Generator

1. Ultrasound device is implantable, MR-compatible, no energy source
2. Power supplied by needle connection
3. External generator used for US-activation and treatment control

Preclinical trials – Short term safety

Rabbits

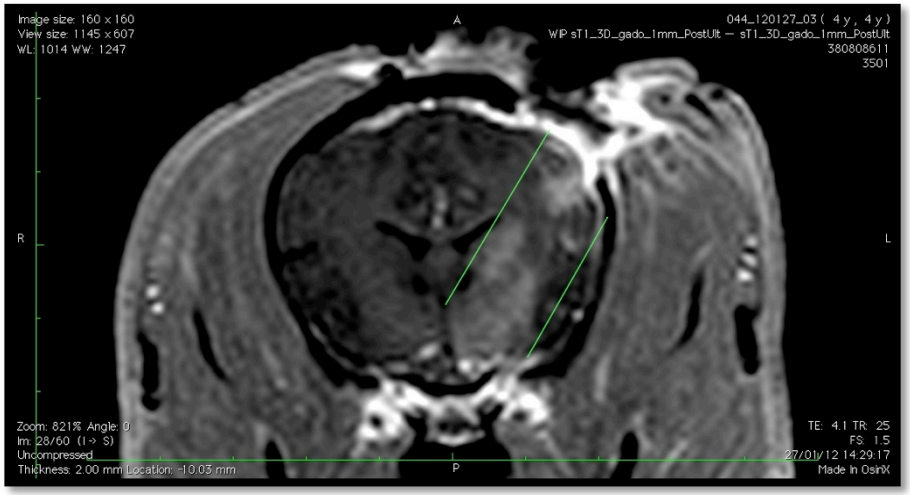


Beccaria et al. Journal of Neurosurgery 2013

Toxicity after 7 days evaluated after BBB opening.

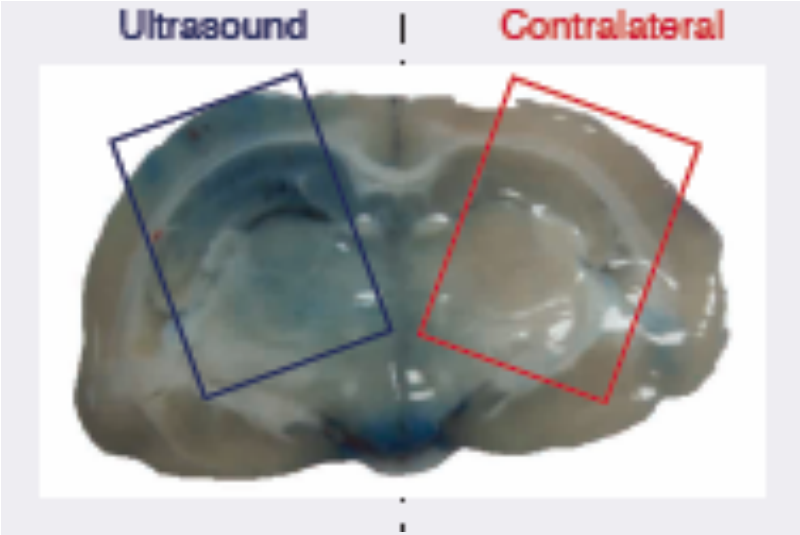
Dogs

No adverse effects observed on MR and histology.
No behavior modification.
MR at day 7 showed normal BBB.

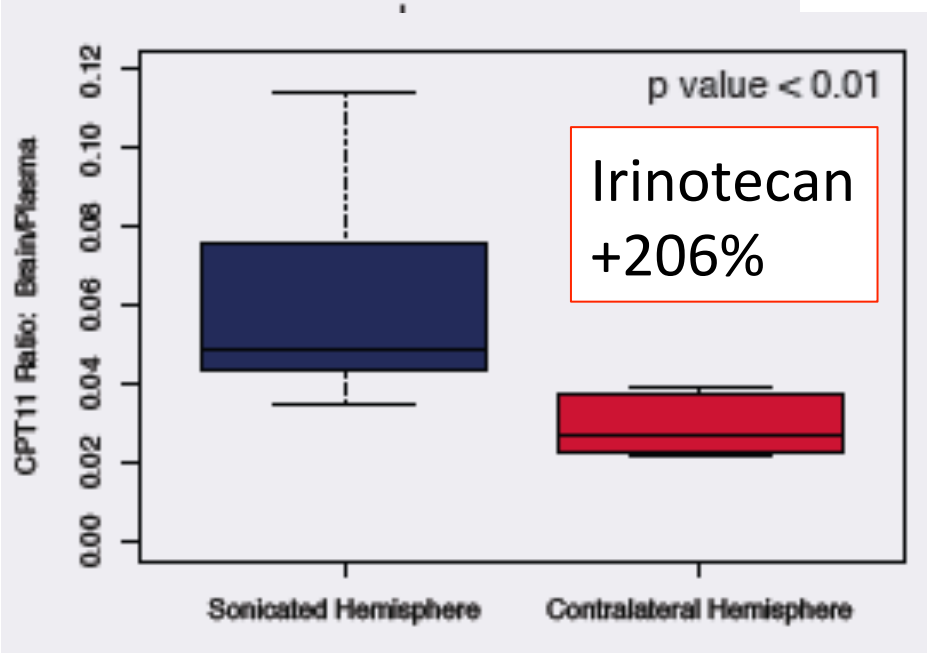


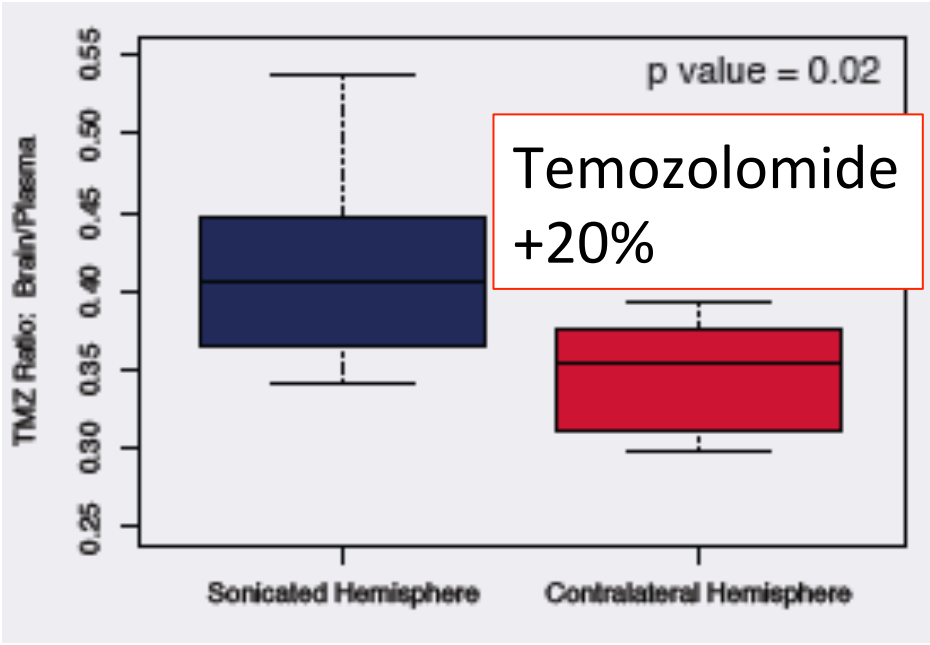
Previous pre-clinical studies show safety of BBB opening protocol in short-term (0-7 days) with single sonication/opening

Preclinical trials – Drug delivery



- Experiments in rabbits
- Opening of the BBB with US 5 minutes after injection of chemotherapy





Goal of the present study

- Perform repeated (7 times) BBB opening
- Evaluate long term safety and toxicity
- in primates

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Experimental protocol

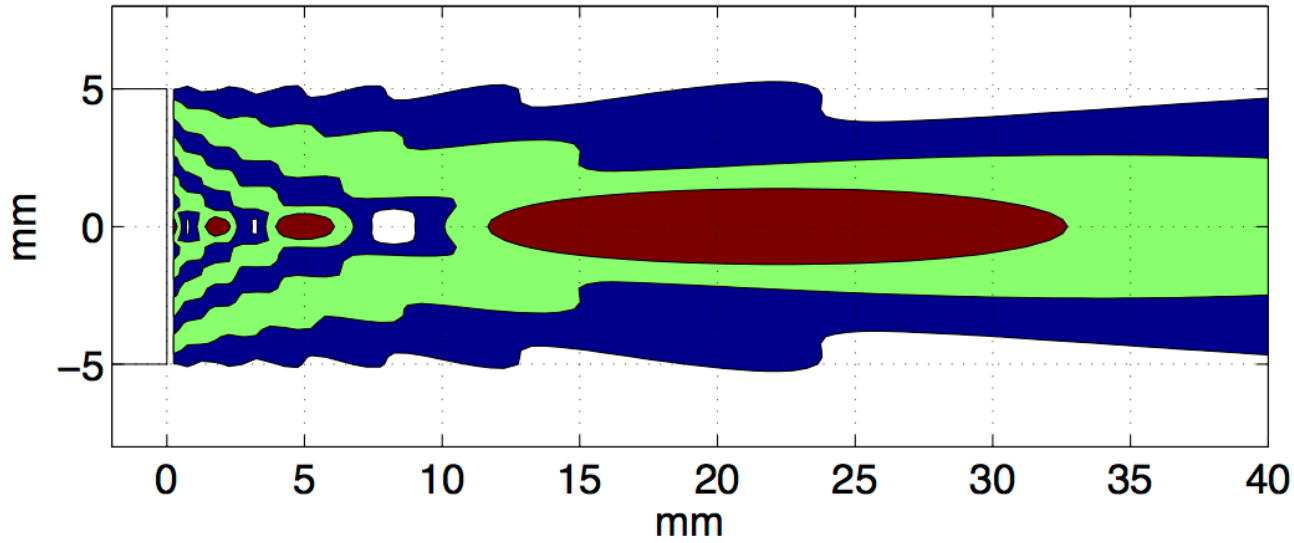
- 3 primates (2 baboons and 1 macaque)

- Protocol:
  - Implantable ultrasound device on top of motor cortex in a typical neurosurgeon's burr hole
  - Repeated BBB openings every 2 weeks during 3 months (7 BBB opening sessions)

- Follow up
  - Contrast enhanced MRI
  - Electrophysiology
  - PET
  - Histology

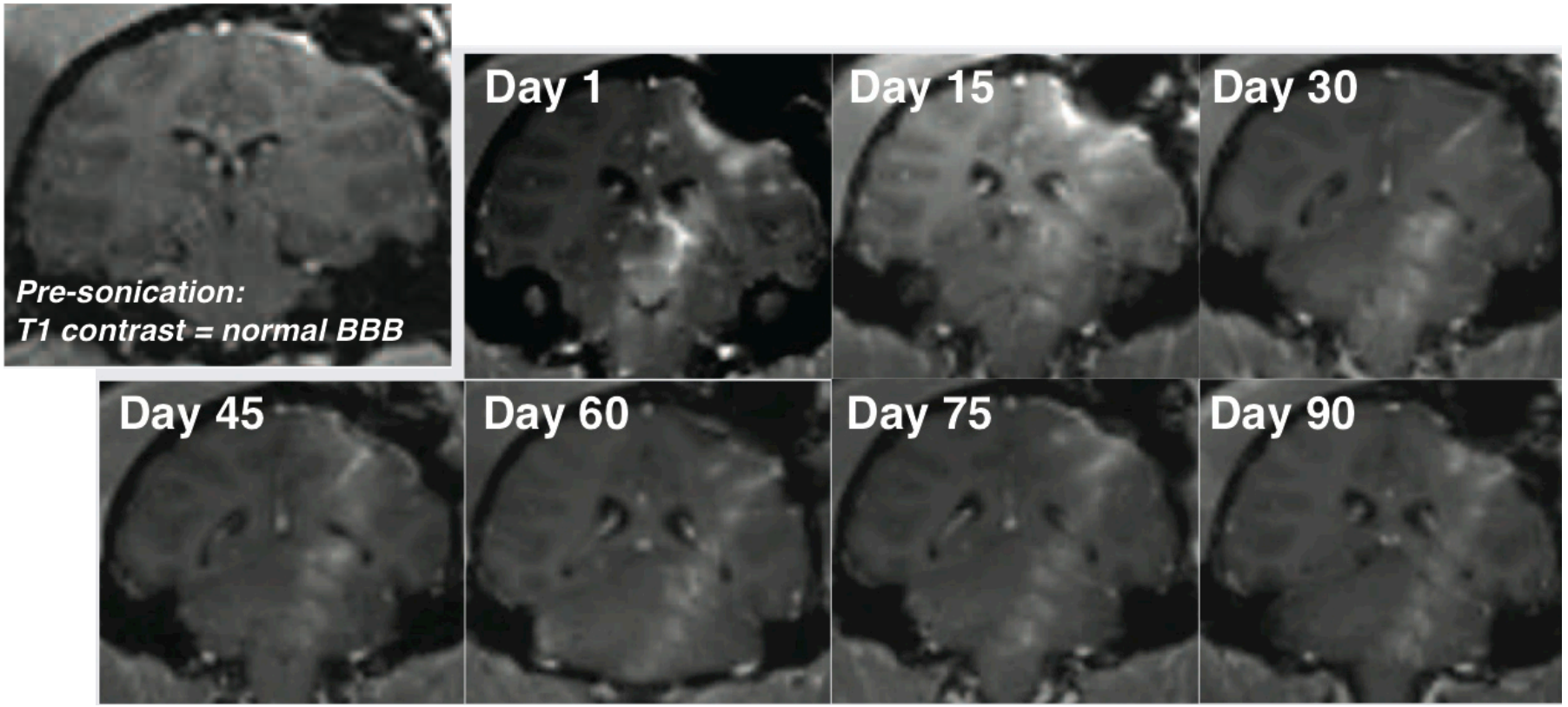
Exposure conditions

- Transdermal electrical supply at each session
- Flat piston, 1 cm in diameter, 1 MHz
- 0.6-0.8 MPa, 25 ms pulse, 1 Hz (DC=2.5%), 120 s
- SonoVue (0.1 cc/kg)



Simulated pressure field in water

Monitoring with T1-w contrast-enhanced MRI

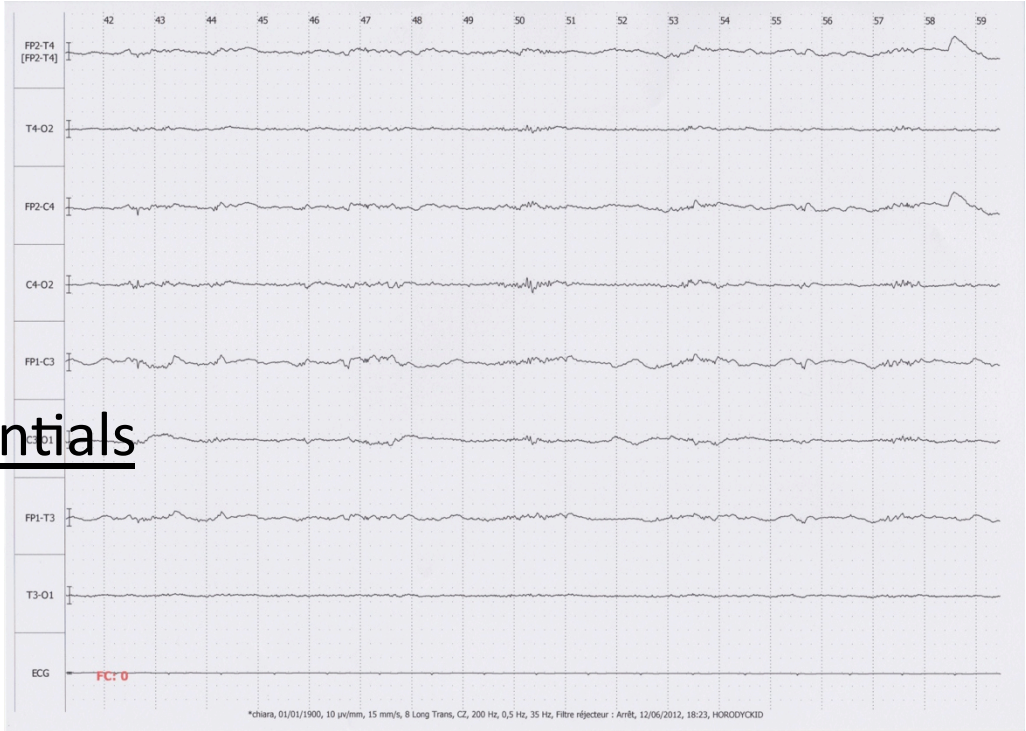


BBB opening observed immediately after each sonication

Electrophysiologic monitoring

Before and after each BBB opening session

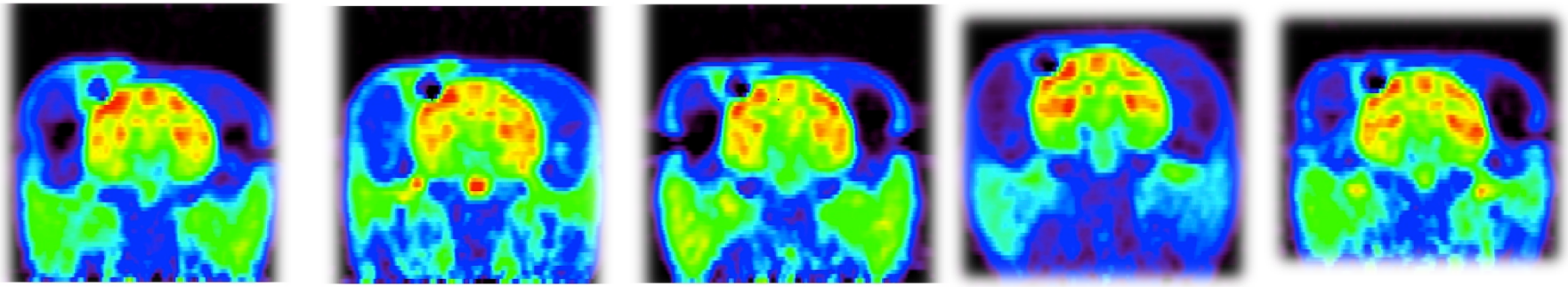
- <u>Electro-Encephalogram</u>
  - No epileptic signs (foci, ii-spike)
  - No cognitive decline
  - No medicinal encephalopathy
- <u>Somatosensory Evoked Potentials</u>
  - No pathologic conduction
  - No amplitude modification



►► No neural hyper excitability
►► No neural conduction abnormality

FDG_{18} / glucose uptake PET monitoring

Day 0 Day 1 Day 45 Day 60 Day 75

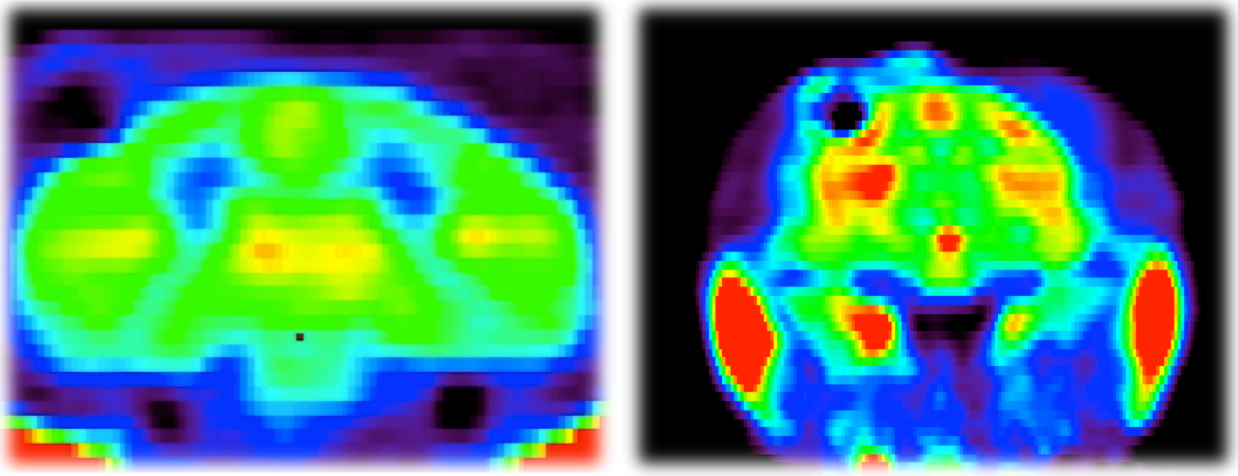


(n=15, after BBB opening)

▸▸ PET scans showed no significant changes in cerebral metabolism of glucose

DPA$_{714}$ PET monitoring

- At D7 post BBB opening



▸▸ No significant inflammation at 7 days post US/BBB opening

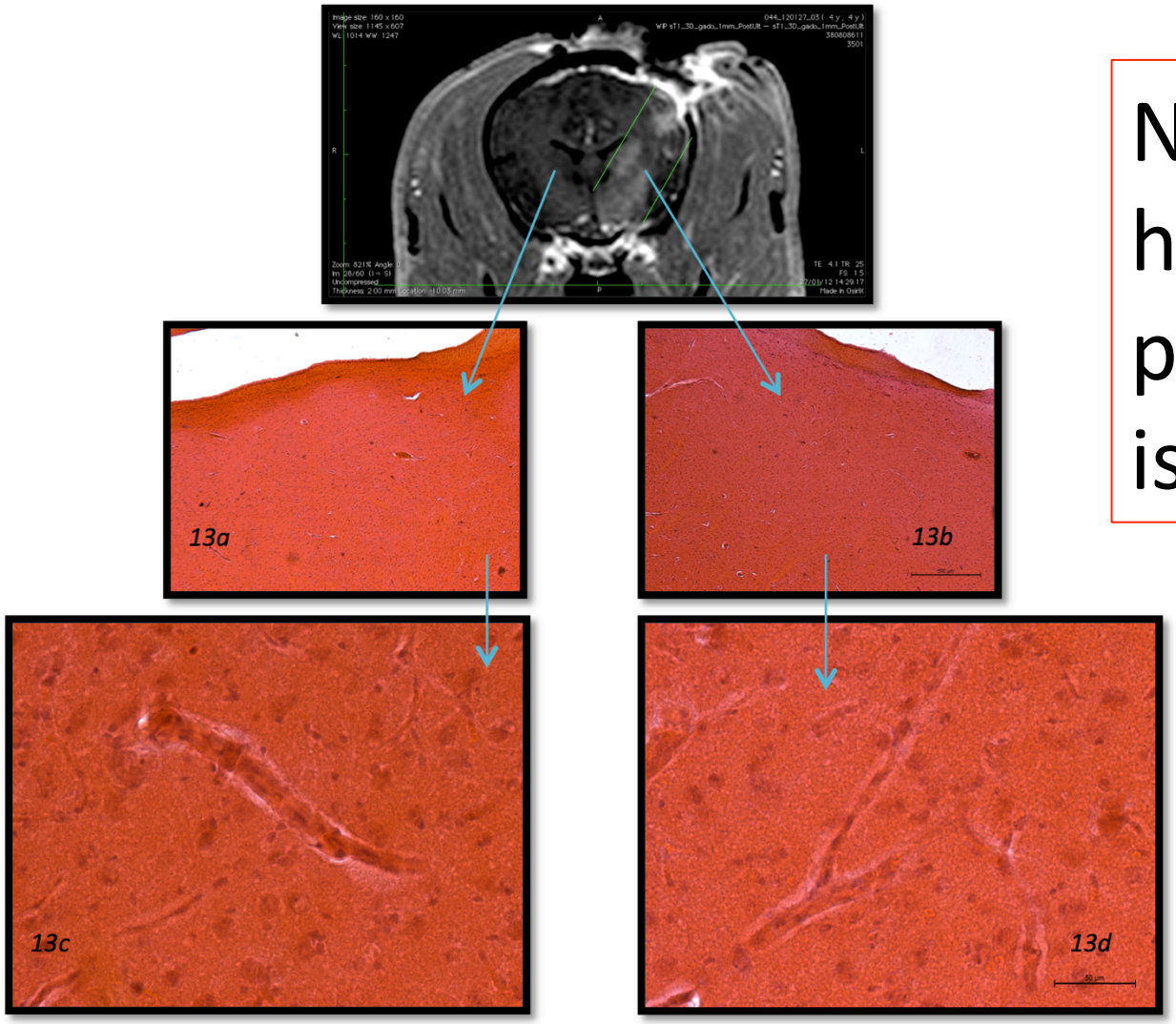
Behavior & Neurological status

- n=3x16: baseline, before and after 7 sonications, endline
- BBB opening was performed in the primary motor cortex

►► Normal Behavior in all 3 animals during the 4 months

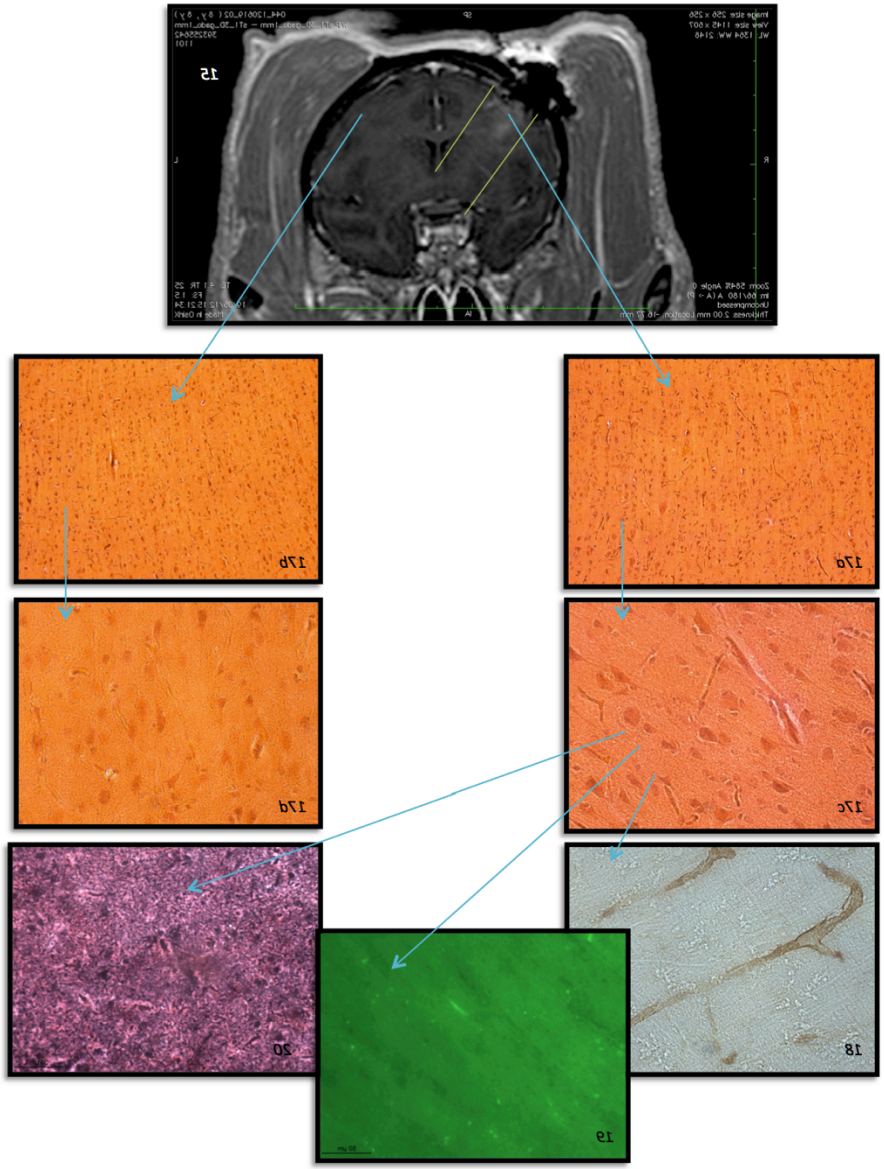
►► Normal motricity neurological status

Histology H&E at month 4



No signs of hemorrhagic processes or ischemia

Histology Glut 1 at month 4



- Integrity of the vessel walls was unchanged.
- Extravasation of a few red blood cells in 1 primate though not observed on MRI.

Conclusions

SonoCloud® : an promising (efficient and safe) implantable ultrasound device developed for repeated BBB opening on clinical routine patients

- Work supported by CarThera SAS

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- CEA Orsay : Raphaeal Boisgard, Geraldine Pottier
- Electrophysiologist : Pr Willer and Dr Huberfeld
- Radiologist : Dr Drier
- Brain & Spine Institute Histopathology : Annick Prigent, Pr Clovis Adam
- Brain & Spine Institute MRI and veterinary teams.