HEMISFER

Hybrid Eeg-MrI and Simultaneous neuro-FEedback for brain Rehabilitation

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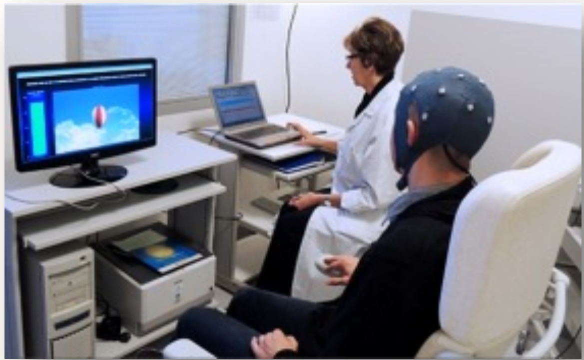
General/initial objectives of HEMISFER

- Make full use of neurofeedback (NF) paradigm for brain self-regulation/stimulation in :
  - rehabilitation (Stokes, ...)
  - psychiatric disorders (resistant mood disorders, anxiety, schizophrenia, ...)
- Main Challenges:
  - Build a real-time computational platform able to implement the Hemisfer concept under a demanding MRI environment
  - Propose new multimodal Neurofeedback paradigms
  - Learn a coupling model associating functional and metabolic information from simultaneous Magnetic Resonance Imaging (fMRI) and Electro-encephalography (EEG)
  - Enhance the NF paradigm from the coupling model

Neurofeedback (NF)



Acquisition
Brain activity is monitored

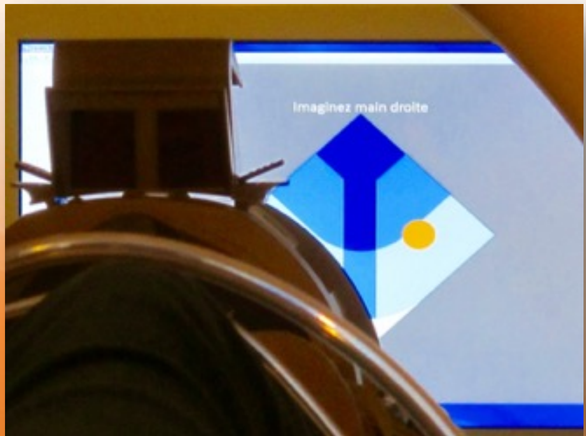
Pre-processing
Signal is cleaned from non neuronal components

REAL-TIME CLOSED LOOP

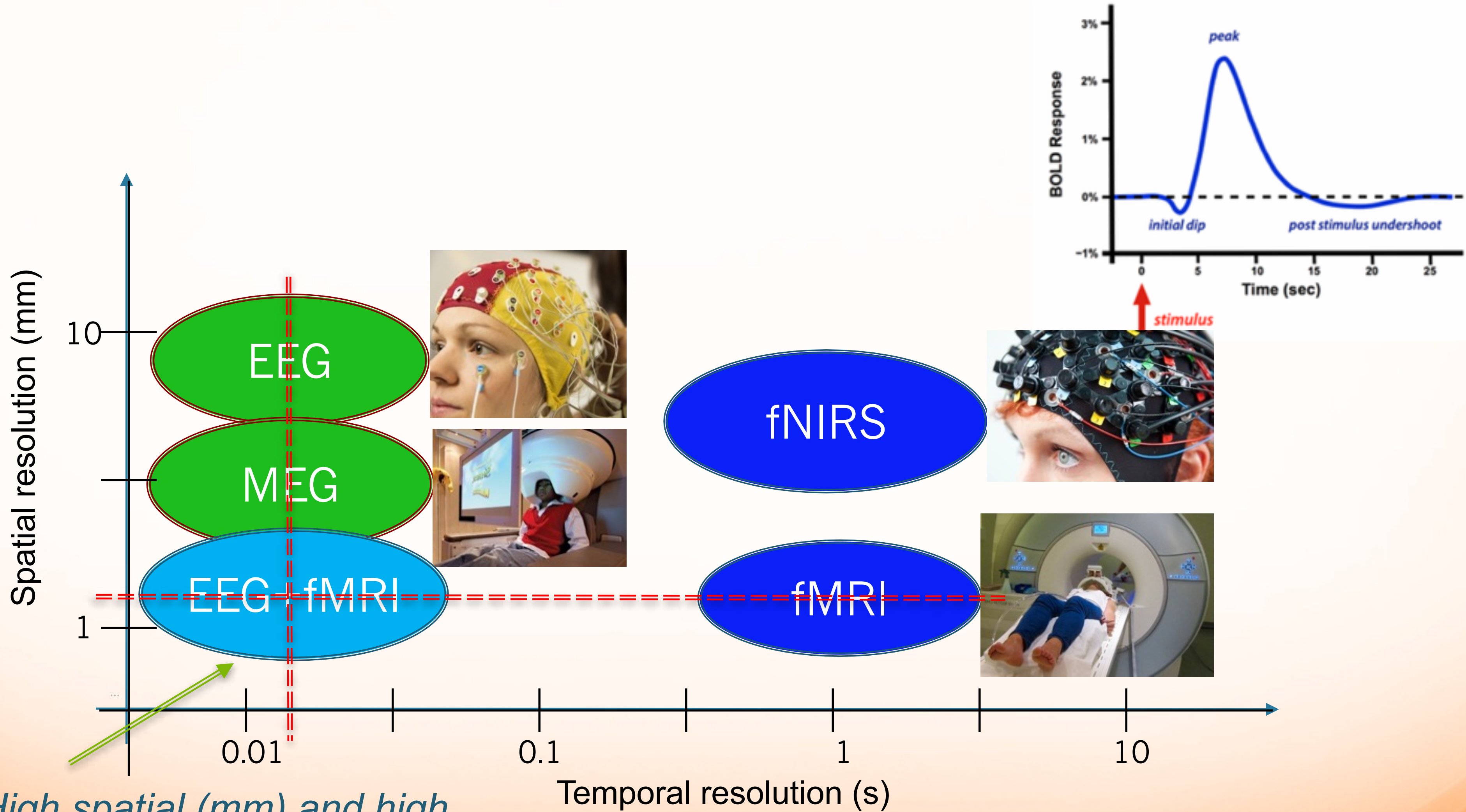
Feature extraction
A feature of interest (related to the function to improve / recover) is extracted

Feedback translation
The feature is returned to the subject through a visual, auditory or tactile feedback

Subject self-regulation
Subject perceives feedback and adapt his mental strategy to control it

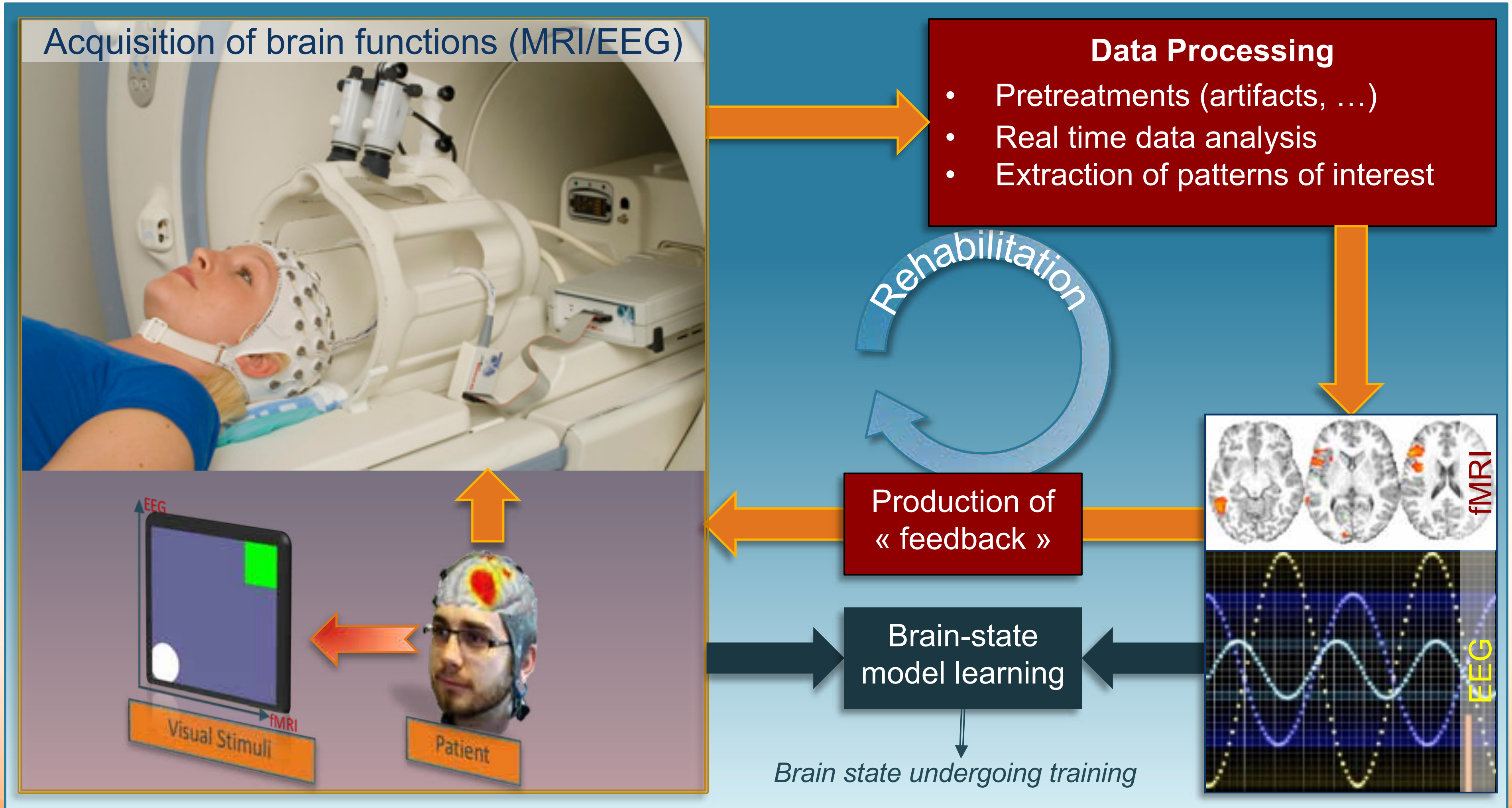


Neurofeedback modalities



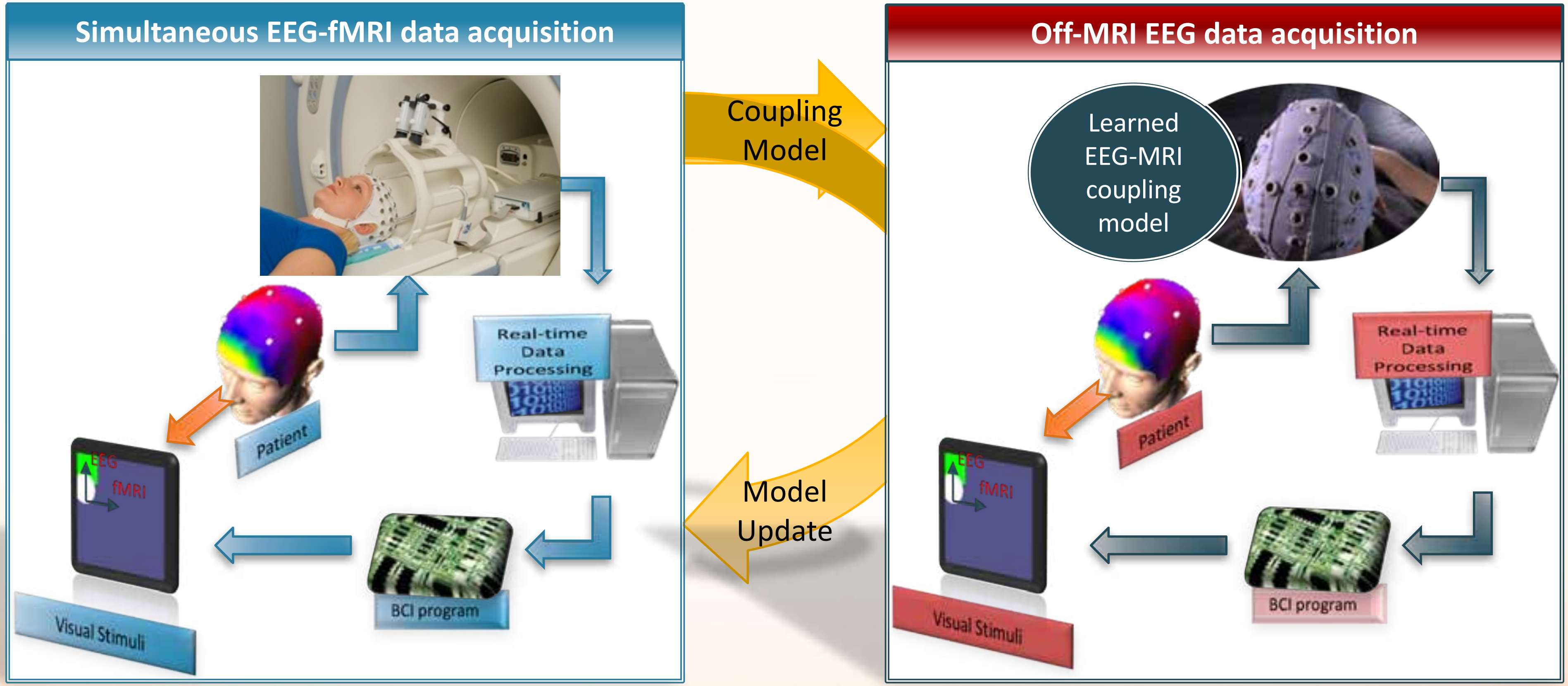
High spatial (mm) and high temporal (ms) resolution

From imaging biomarkers to new therapeutic solutions: The HEMISFER Project



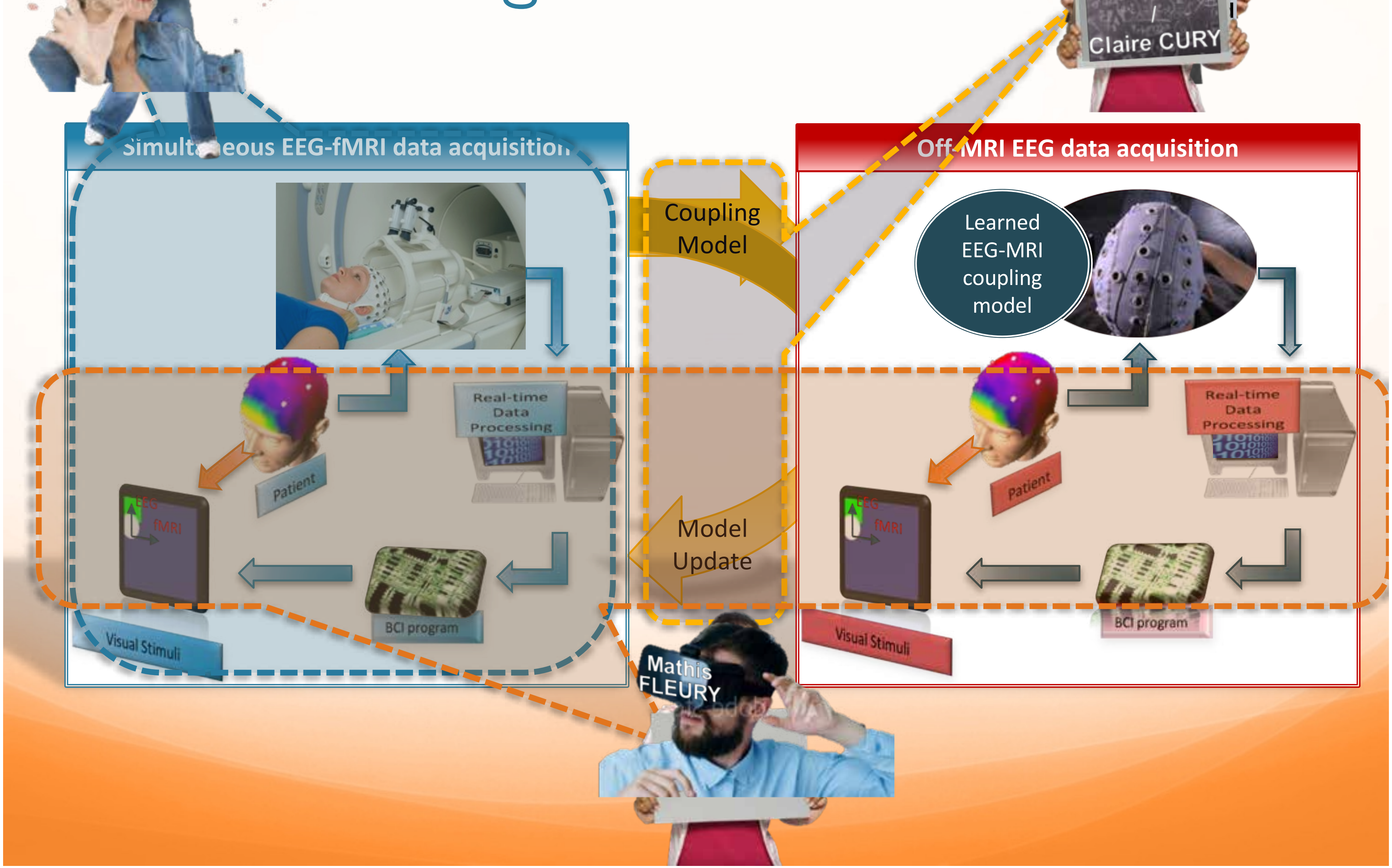
Neurofeedback (NF) is defined as the self-regulated change of a particular brain activity that is reflected in the change of one or several neurosignals captured by brain activity measurement technologies such as electroencephalography (EEG), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), or near-infrared spectroscopy (NIRS).

HEMISFER project: From imaging biomarker to image-guided therapy



- Joint project with Visages, PANAMA and HYBRID teams and Univ. Hosp. and Psychiatric Hosp. of Rennes
- Applications: Make full use of neurofeedback (NF) paradigm for brain self-regulation/stimulation in:
  - rehabilitation (ADHD, Stokes, ...)
  - psychiatric disorders (resistant mood disorders, anxiety, schizophrenia, ...)

HEMISFER project organization



Added value of collaboration

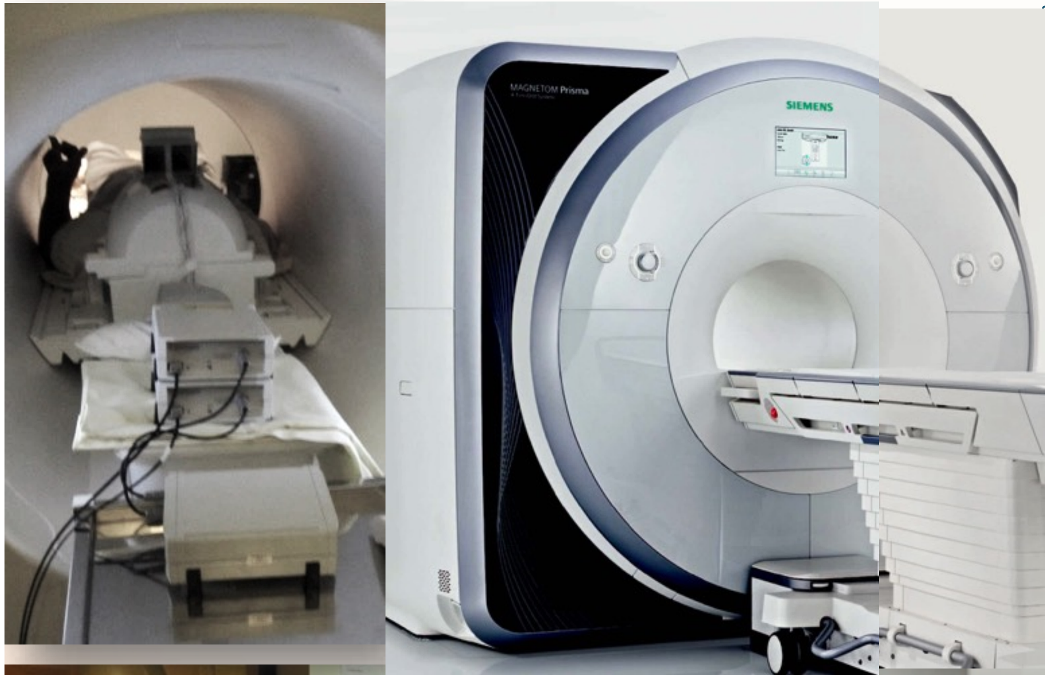
- Joint project with Visages, PANAMA and HYBRID teams, the Univ. Hosp. and Psychiatric Hosp. of Rennes, plus the ATHENA team (Inria Sophia)

Signal & image processing and machine learning	→	PANAMA and VISAGES teams
BCI and EEG processing	→	HYBRID and VISAGES teams along with ATHENA team
Real-time processing of fMRI (BOLD and ASL)	→	VISAGES and HYBRID Teams along with Neurinfo
Clinical Research	→	VISAGES, HYBRID and EA 4712 teams

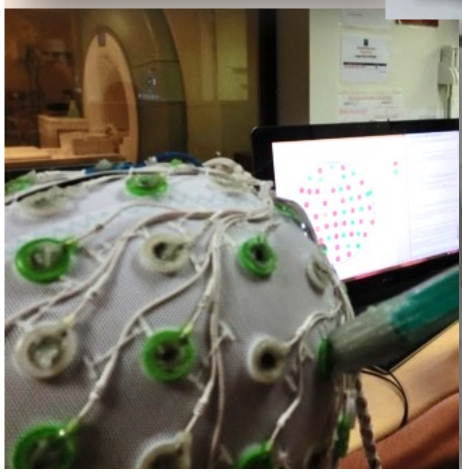
- All people are co-supervised by at least two research groups

- Potential industrial collaboration (*long term*):
  - Clinical research: Biotrial
  - BCI and software integration: Mensia Tech.

Experimental Environment: The Neurinfo Platform

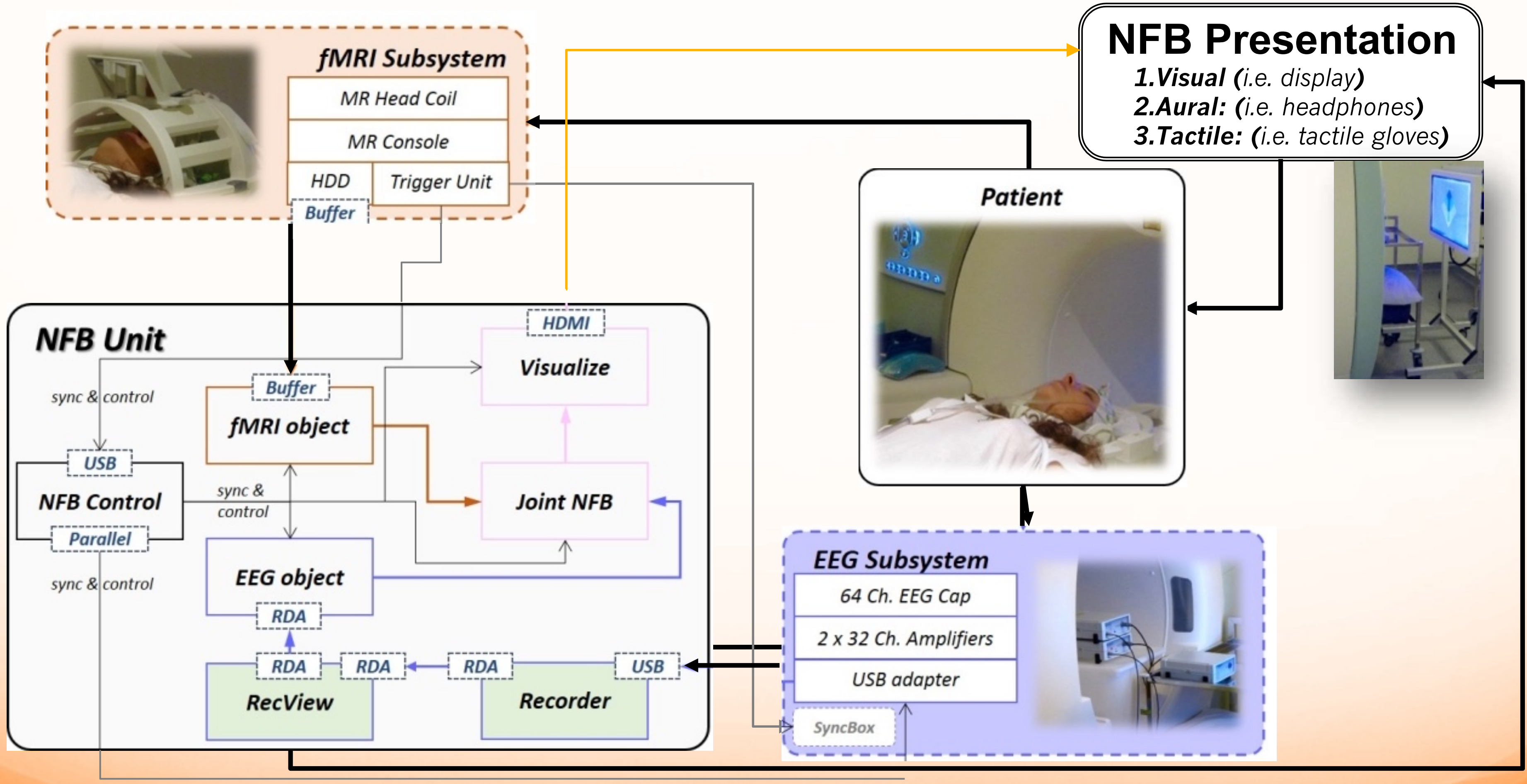


- 3T Verio by SIEMENS → 3T PRISMA (Q1-2018):
  - 60 cm Diameters– Length 198cm
  - 10 tons,
  - side positioning
  - Field of View : 50 x 50 x 50 cm
  - Gradients 80mT/m @ 200T/m/s, @400μs
  - 128 independent channels
  - Field homogeneity :
    - <0.1 ppm/h
    - 0,1 ppm (@ 40 cm)
    - 0,045ppm (@ 30 cm)
- MR-EEG BrainProducts 64 channels system



#1. The Hybrid EEG-MRI Neurofeedback system @ Neurinfo

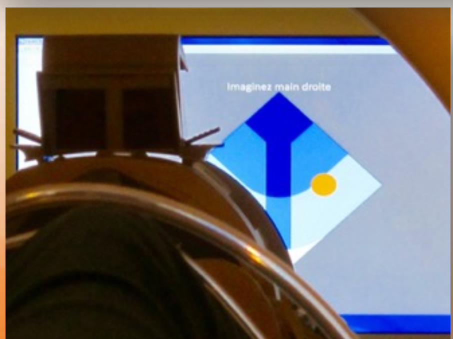
CominLabs

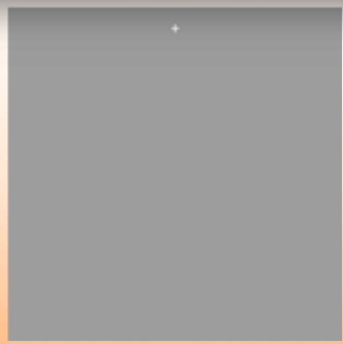


[Mano et al, OHBM 2016, Frontiers in Neurosciences 2017, Patent 2017]

#1. Computational Platform Experiments and Results

Results



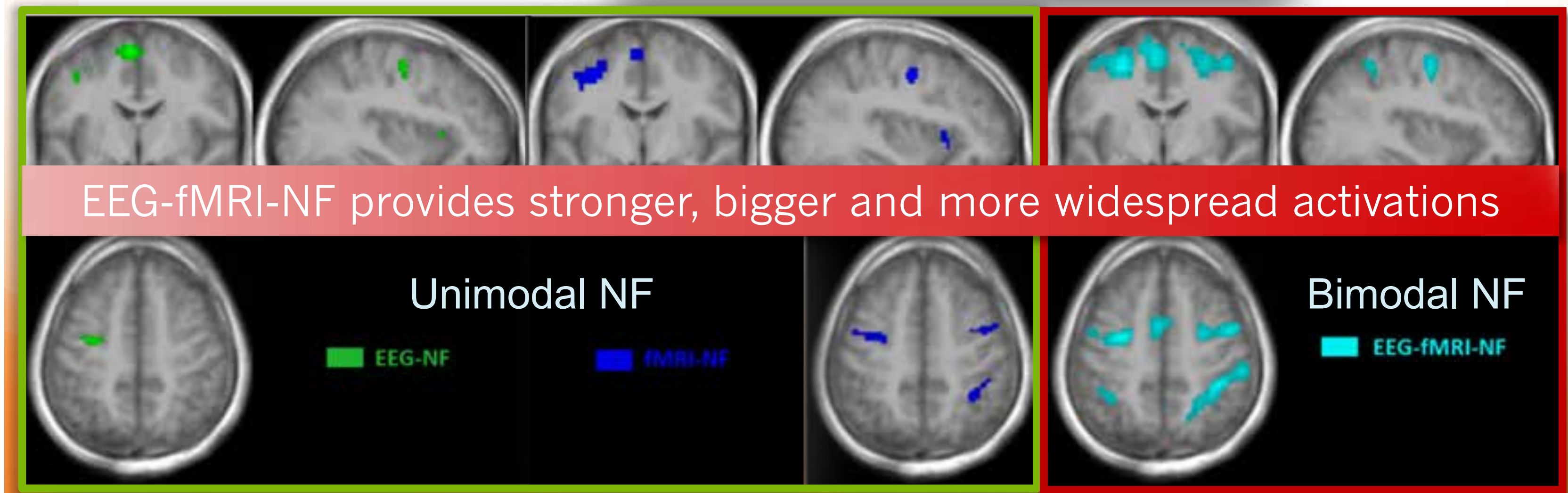


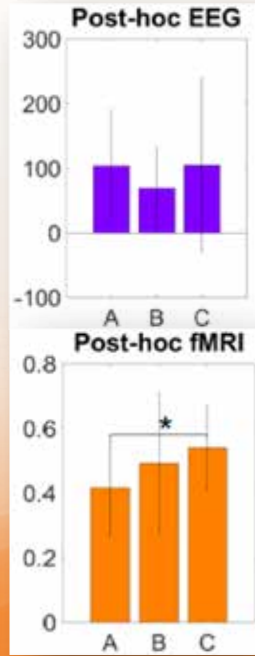
- Our platform showed very good real-time performance when tested with various pre-processing, filtering, and NF estimation and visualization methods.
- The entire fMRI processing from acquisition to NF estimation in all scenarios takes less than 200ms, well below the TR of regular MRI sequences (2s). The same processing for EEG, is done at 2ms (~50Hz).
- Various NF tasks scenarios for regulating the measured brain activity were tested with subjects and patients. In particular, the platform was used for a NF study on motor imagery related brain activity.

#2. Experiment study n°1: EEG-fMRI neurofeedback of a motor imagery task

- **Motivation:** Proof-of-Concept of HEMISFER
- **Challenge:**
  - Able to provide real-time neurofeedback (NF) from simultaneous EEG/fMRI real-time recording on motor imagery (never done)
  - Investigate new neurofeedback hybrid paradigm
- **Contributions:**
  - Use the real-time processing environment
  - Propose a new bimodal NF paradigm
  - Experimented on 10 normal controls
  - Confirm Hypothesis :
    - *EEG activations* : *EEG-NF* ≥ *EEG-fMRI-NF* > *fMRI-NF*
    - *fMRI activations* : *fMRI-NF* ≥ *EEG-fMRI-NF* > *EEG-NF*

Recorded multimodal EEG/fMRI NF



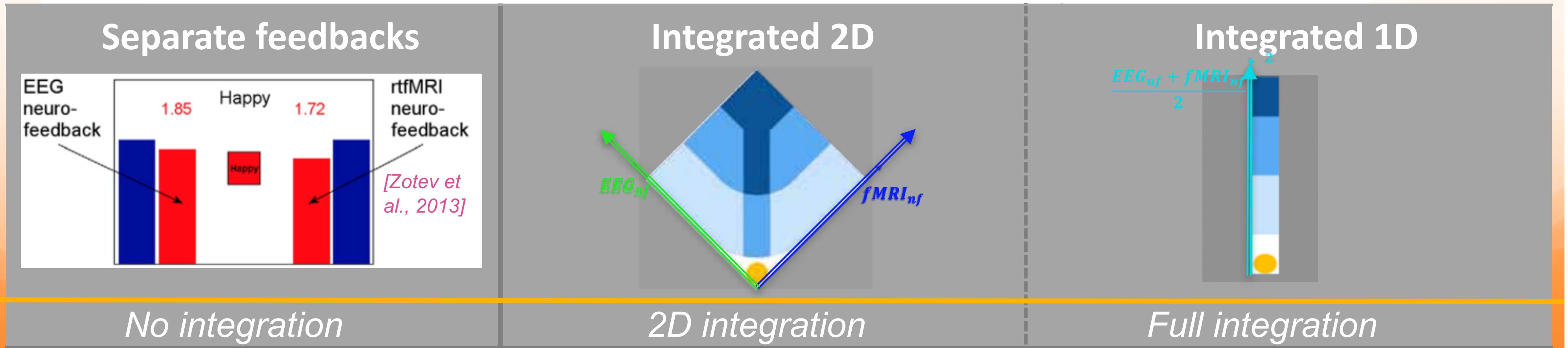


[Perronnet et al, OHBM 2016, Frontiers in Neurosciences 2017]

#2. Experiment study n°2: Towards integrated EEG-fMRI neurofeedback

CominLabs

- **Motivation:** How to represent multiple EEG and fMRI features simultaneously?
- **Challenge:**
  - Problem of separate feedbacks:
    - Potential concurrent brain regulation tasks
    - Cognitive load
- **Contributions:**
  - Integration of the EEG and fMRI features into a single feedback
  - Compare 1-D versus 2-D metaphors
  - Experimented on 20 normal controls (2 groups of 10)



[Perronnet et al, Neuroimage 2018, *under revision*]

#2. Experiment study n°2: Towards integrated EEG-fMRI neurofeedback

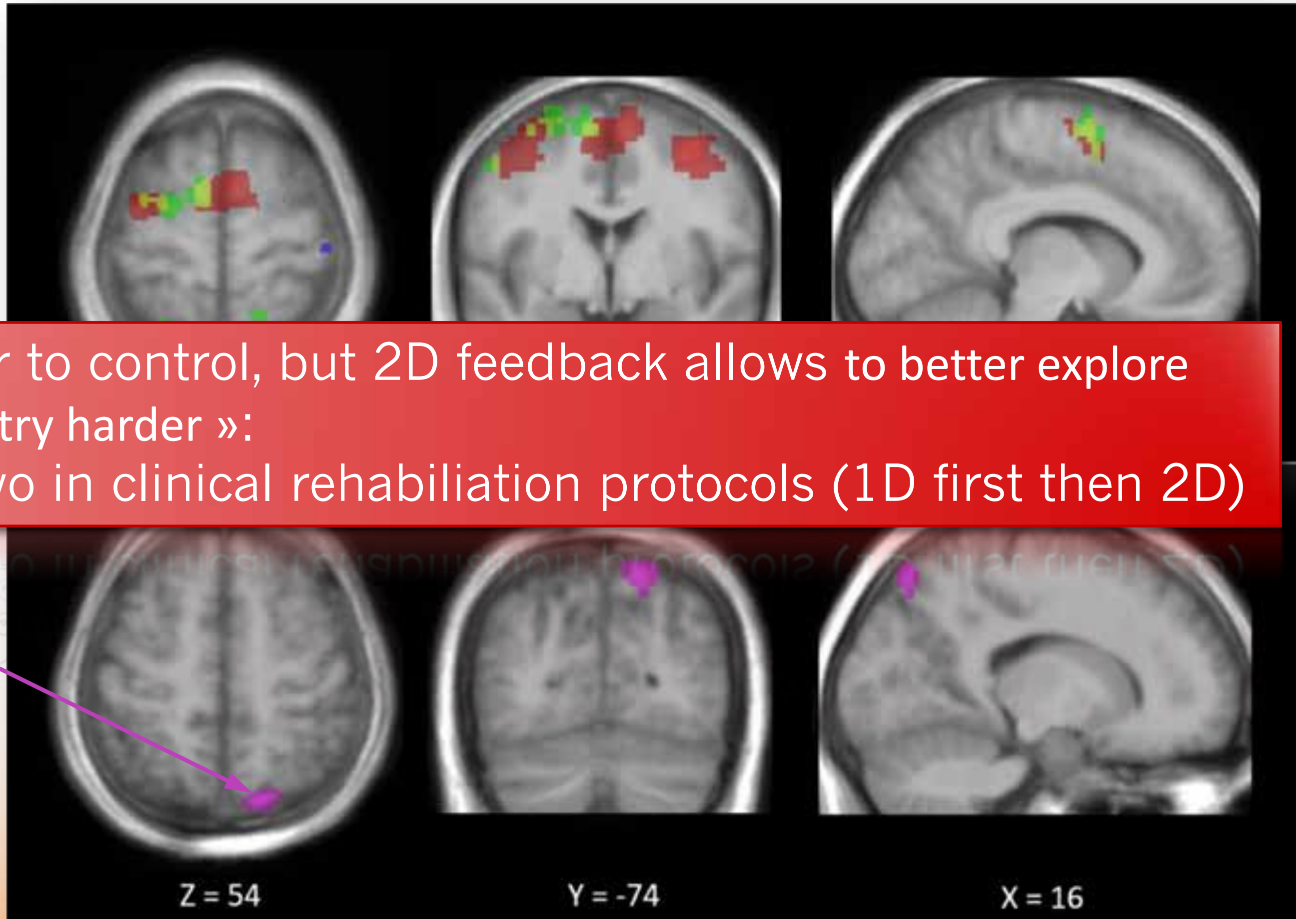
CominLabs

- **Motivation:** How to represent multiple EEG and fMRI features simultaneously?
- **Results :**

1D activation

2D activation

2D deactivation



1D feedback is easier to control, but 2D feedback allows to better explore mental strategies and « try harder »:

⇒ Alternate the two in clinical rehabiliation protocols (1D first then 2D)

More activations are found in the 2D group in the right **superior parietal lobule** (SPL)

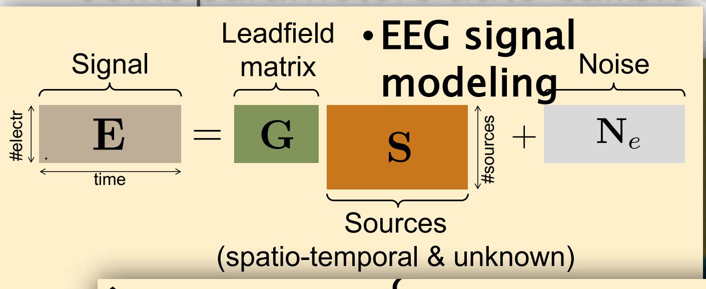
2D > 1D

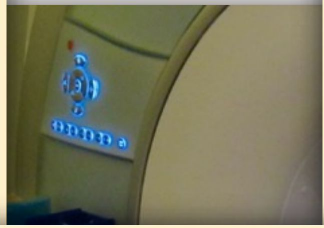
($p < 0.001$, uncorrected)

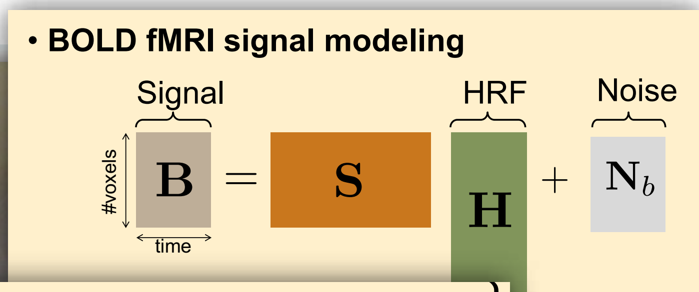
[Perronnet et al, Neuroimage 2018, *under revision*]

#3. Coupling model : Joint Source Estimation of EEG and fMRI

- Challenges:
  - Joint EEG and fMRI reconstruction to achieve high spatial AND temporal resolution
- Contributions:
  - Joint reconstruction imposing sparsity constraints
  - Joint parameters auto-calibration







$$\hat{\mathbf{S}} = \underset{\mathbf{S}}{\operatorname{argmin}} \left\{ \alpha ||\mathbf{GS}-\mathbf{E}||_2^2 + (1-\alpha)||\mathbf{SH}-\mathbf{B}||_2^2 + \lambda ||\mathbf{S}||_1 \right\}$$

- **Joint Reconstruction**
  - The L_1 penalty term is enforcing sparsity of sources.
  - Minimization : proximal algorithm & Iterative Soft Thresholding
- **Parameter calibration**
  - The two fidelity terms have different orders of magnitude.
  - α is then difficult to adjust.
  - Each term is therefore first calibrated/normalized based on unimodal data.

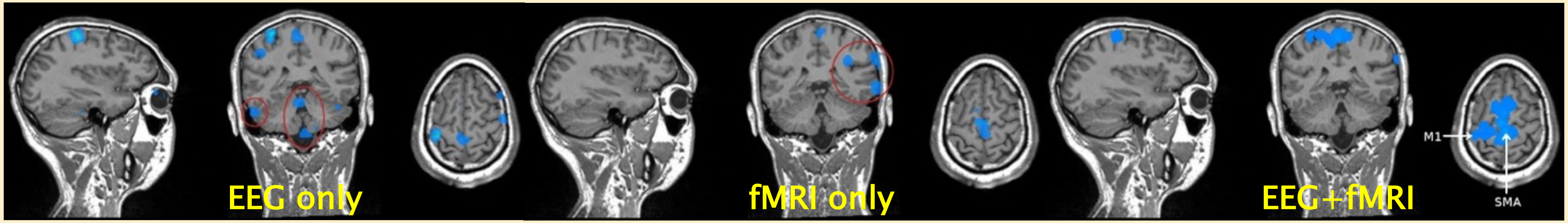
[Oberlin *et al*. EUSIPCO 2015; Noorzadeh *et al*., MICCAI 2017]

#3. Coupling model : Joint Source Estimation of EEG and fMRI

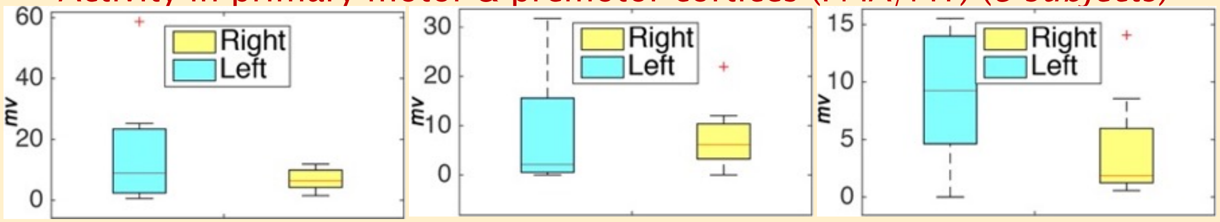
CominLabs

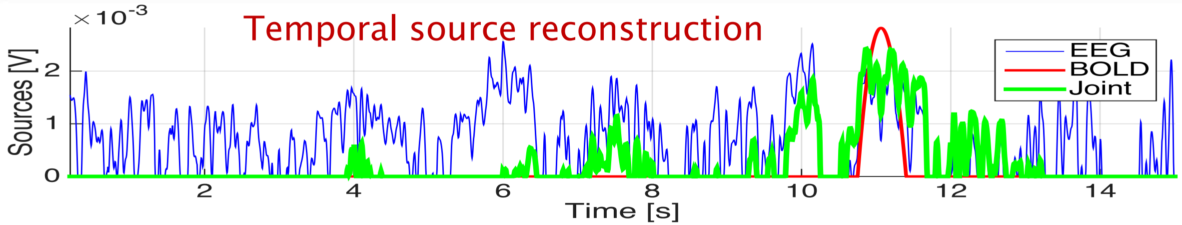
- Challenges:
  - Joint EEG and fMRI reconstruction to achieve high spatial AND temporal resolution
- Results:
  - Experiments to compare EEG-only, fMRI-only and EEG+fMRI sources estimation

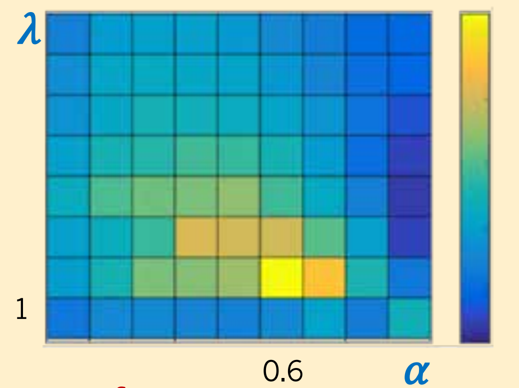
Active sources (*one subject*)



Activity in primary motor & premotor cortices (PMA/M1) (*8 subjects*)







Performance score w.r.t. calibration parameters α and λ

[Oberlin *et al.* EUSIPCO 2015; Noorzadeh *et al.*, MICCAI 2017]

More to come: Hemisfer clinical

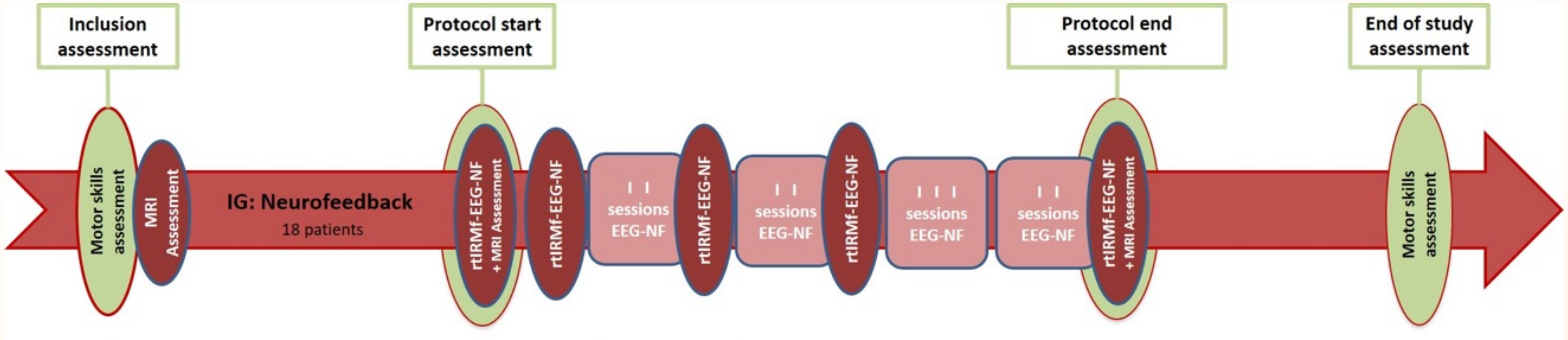
CominLabs

- **Move from proof-of-concept to "real word"**
- **Depression protocol : « Neurofeedback techniques in the therapy of resistant mood disorders »**
  - Objective: To explore the neurofeedback technique potential on the intensity of mood disorders for patients poorly responsive to current pharmacological and psychotherapeutic techniques.
- **Additional support** from "Fondation pour le Recherche Médicale" (350k€ for 4 years)
- **Stroke Protocol : « Effect of NeuroFeedback combining in real-time EEG and fMRI on upper limb motor rehabilitation after stroke »**
  - **Objective of the clinical study**: Evaluate the effect of Neurofeedback treatment on the cerebral plasticity and the motricity of the upper limb after a stroke event.
  - **Rationale**:
    - rtfMRI-EEG Neurofeedback has been tested <u>once</u> on depression patients but never on stroke one.
    - A bimodal neurofeedback would be more specific and would allow a better motor rehabilitation due to the neuronal reorganization of the sensori-motor cortex (*Wang, T., Mantini, D. & Gillebert, C. R. The potential of real-time fMRI neurofeedback for stroke rehabilitation: a systematic review. Cortex, 2017*)
  - **Protocol**:
    - Prospective, randomized study with 2 groups (30 patients):
      - Interventional group (18 patients) with rtfMRI-EEG-NF & EEG-NF
      - Control group (12 patients) with Motor Imagery task only (monitored by EEG)

More to come: Hemisfer clinical

CominLabs

- **Move from proof-of-concept to "real word"**
- **Stroke Protocol : « Effect of NeuroFeedback combining in real-time EEG and fMRI on upper limb motor rehabilitation after stroke »**
  - **Challenge**: To test the efficiency of a neurofeedback rehabilitation program for chronic stroke patients with severe to moderate recovery of motor skills of their upper limb.



Some numbers

- Patients inclusion duration : 1 year
- Duration of the study per patient : 3 months
- **Overall 520h of experimental work**
  - 144 MRI sessions (~120h)
  - 330 EEG-NF/EEG-IM sessions (~ 165h)
  - Clinical evaluation of motor disability: 240h
- **Total budget for the study : 150k€ (5k€/patient)**

Hemisfer: Current Summary

CominLabs

- Project actually started on Jan 2014
- Major Originalities:
  - The “theragnostic” concept: translate imaging sensors to therapeutic systems
  - Hemisfer paradigm never addressed before
  - Joint fMRI/EEG for Neurofeedback addressed only very recently by one team in 2014 (*not afterwards*)
  - EEG/fMRI coupling model from machine learning and sparse representation has never been addressed before
- Major opportunities:
  - High integration of the work between the Hemisfer partners (from information processing, brain computer interface to clinical medicine)
  - Two major clinical applications : same generic technology applied to two very different clinical rehabilitation domains
  - Ancillary opportunity: *observe the pathological brain under evolution (e.g. Epilepsy, Cognition)*
- High efficiency of the collaboration:
  - All dedicated people are shared between at least two teams
  - Effective cross-fertilization between different domains (signal & image processing, VR & Virtual interfaces, medicine)
- Actual outcomes
  - Technological aspects:
    - integration of a new MR-compatible EEG system (Brain Product)
    - Integration of real time processing for the EEG/fMRI system (first in-vivo experiments done) (*one patent*)
    - One of the first world-wide study for safety compatibility of simultaneous ASL/EEG recording [*ISMRM & SFRMBM 2015]*

Hemisfer: Current Publications

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- Coupling EEG and fMRI
  - Noorzadeh, S., Maurel, P., Oberlin, T., Gribonval, R., Barillot, C., 2017. Multi-modal EEG and fMRI Source Estimation Using Sparse Constraints. MICCAI 2017 - 20th International Conference on Medical Image Computing and Computer Assisted Intervention, Quebec, Canada.
  - Oberlin, T., Barillot, C., Gribonval, R., Maurel, P., 2015. Symmetrical EEG-FMRI Imaging by Sparse Regularization. European Signal and Image Processing Conference - EUSIPCO 2015. IEEE, pp. 1-5.
- Platform
  - [**Patent**] Mano, M., Perronnet, L., Lecuyer, A., Barillot, C., 2016. Hybrid Eeg-MrI and Simultaneous neuro-feedback for brain Rehabilitation. In: Inria (Ed.). CNRS, INRIA, France
  - Mano, M., Lecuyer, A., Bannier, E., Perronnet, L., Noorzadeh, S., Barillot, C., 2017. How to Build a Hybrid Neurofeedback Platform Combining EEG and fMRI. Front Neurosci 11, 140.
  - Mano, M., Bannier, E., Perronnet, L., Lécuyer, A., Barillot, C., 2017. Hybrid EEG and fMRI platform for multi-modal neurofeedback. International Society of Magnetic Resonance in Medicine. ISMRM, Honolulu, United States, p. 4550.
  - Mano, M., Bannier, E., Perronnet, L., Lécuyer, A., Barillot, C., 2016. Design of an Experimental Platform for Hybrid EEG-fMRI Neurofeedback Studies. 22nd Annual Meeting of Human Brain Mapping, Geneva, CH, p. 2078.
- Neurofeedback
  - G. Lioi, M. Fleury, S. Butet, A. Lécuyer, C. Barillot, I. Bonan (2018) - Bimodal EEG-fMRI Neurofeedback for Stroke Rehabilitation: a Case Report – ISPRM 2018 (*clinical abstract*)
  - L Perronnet, A Lécuyer, M Mano, F Lotte, M Clerc, C Barillot (2018). Learning 2-in-1: towards integrated EEG-fMRI-NF. Neuroimage [under revision].
  - Perronnet, L., Lecuyer, A., Mano, M., Bannier, E., Lotte, F., Clerc, M., Barillot, C., 2017. Unimodal Versus Bimodal EEG-fMRI Neurofeedback of a Motor Imagery Task. Front Hum Neurosci 11, 193.
  - Perronnet, L., Lécuyer, A., Mano, M., Bannier, E., Lotte, F., Clerc, M., Barillot, C., 2016. Hybrid EEG-fMRI neurofeedback of a motor-imagery task. 22nd Annual Meeting of Human Brain Mapping, Geneva, CH, p. 4133.
  - Perronnet, L., Lécuyer, A., Lotte, F., Clerc, M., Barillot, C., 2016. Brain training with neurofeedback. In: Clerc, M., Bougrain, L., Lotte, F. (Eds.), Brain-Computer Interfaces / Les Interfaces Cerveau-Ordinateur. ISTE-Wiley, pp. 291-309.
  - Perronnet, L., Lécuyer, A., Lotte, F., Clerc, M., Barillot, C., 2016. Entraîner son cerveau avec le neurofeedback. In: Maureen, C., Laurent, B., Fabien, L. (Eds.), Les interfaces cerveau-ordinateur 1. ISTE editions, pp. 277-292.
- Misc.
  - Bannier, E., Mano, M., Robert, S., Corouge, I., Perronnet, L., Lindgren, J., . . . Barillot, C., 2015. On the feasibility and specificity of simultaneous EEG and ASL MRI at 3T. ISMRM, Toronto, Canada.
  - Bannier, E., Mano, M., Robert, S., Corouge, I., Perronnet, L., Lindgren, J., . . . Barillot, C., 2015. Faisabilité et spécificités de l'ASL-EEG simultané à 3T. SFRMBM, Grenoble, France.
- Workshop Neurofeedback and Brain Computer Interfaces (Rennes, Sept. 7th, 2017)

THANK YOU FOR YOUR ATTENTION

Acknowledgments

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