Multimodal Neurofeedback

Perspectives

Brain Image Analysis: Arterial Spin Labeling and Joint EEG-fMRI Neurofeedback

Habilitation à diriger des recherches

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Professional Record

- 2005-2009 : PhD/PostDoc on Applied Mathematics / Computer Vision
- Since Sept. 2009 : Maître de conférences (Université de Rennes 1)



- Since 2019 : co-head of the "Imagerie Numérique" training program at ESIR (equivalent to master degree).
- Since 2019 : head of Empenn U1228 (Inria/Inserm/UR1/CNRS), ≈ 30 people

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Supervision Activity



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Brain Perfusion Imaging

Brain Perfusion

Delivery of oxygen and nutrients from the blood to the brain tissue

capillary microcirculation



- Pathological perfusion : reason or consequence of brain pathologies (cerebrovascular disease, oncology, dementia, psychiatric disease, epilepsy)
- several imaging techniques, with different properties
- \rightarrow Arterial Spin Labeling : non-invasive (no-contrast, no-radiation), quantitative

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Arterial Spin Labeling: Acquisition



Magnetic Labeling

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Arterial Spin Labeling: Acquisition



Magnetic Labeling



Delay

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Arterial Spin Labeling: Acquisition



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Delay



Readout

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Delay



Readout



Label Image

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Readout



Label Image



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Readout



Readout



Label Image



Control Image

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Delay



Readout



Readout



Label Image



Control Image

 \rightarrow Obtaining perfusion-weighted images :



Control Image



Label Image



Difference 1 pair

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Arterial Spin Labeling: Acquisition



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Delay



Readout



Readout



Label Image



Control Image

 \rightarrow Obtaining perfusion-weighted images :



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Arterial Spin Labeling: Signal Modeling

• Perfusion imaging, requires no contrast injection



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Arterial Spin Labeling: Signal Modeling

• Perfusion imaging, requires no contrast injection



• Δt : arterial transit time

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Arterial Spin Labeling: Signal Modeling

• Perfusion imaging, requires no contrast injection



- Δt : arterial transit time
- τ : labeling duration / temporal width of the labeling

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Arterial Spin Labeling: Signal Modeling

• Perfusion imaging, requires no contrast injection



- Δt : arterial transit time
- τ : labeling duration / temporal width of the labeling
- TI₂: acquisition time
- \rightarrow Cerebral Blood Flow (CBF) in mL.100g $^{-1}.min^{-1}$

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ASL : pros and cons

Advantages

- non invasive: suitable for healthy subjects, pediatrics, ...
- quantitative: necessary for individual analyses

Limits

- quality of images: low Signal-to-Noise ratio
- individual analyses are **restricted by sensitivity** to noise, motion, arterial artifacts, quantification errors, ...

 \rightarrow need for mathematical/numericals tools

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ASL processing pipeline



Raw ASL Acquisitions

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Robust Estimation of Cerebral Blood Flow

• Sample mean \rightarrow sensitive to outliers (e.g. motion artifacts)







• M-estimator can be used to be less sensitive to outliers

(Maumet et al., 2013b)

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Robust Estimation of Cerebral Blood Flow

Sample mean → sensitive to outliers (e.g. motion artifacts)



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ASL processing pipeline





High-resolution Anatomical Image

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ASL: Patch-Based Super-Resolution



-Q- Contribution (Meurée et al., 2017)

- $\bullet\,$ Fast acquisition techniques are required \rightarrow low resolution and low SNR images
- High-resolution anatomical image



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ASL: Patch-Based Super-Resolution

Similar to the non-local mean denoising method

$$X_i^{t+1} = \frac{1}{Z_i} \sum_{j \in V_i} X_j^t \,\omega_{i,j}^t$$

• $\omega_{i,j} \rightarrow$ weights, patch-based similarity in both perfusion and anatomical

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 X_i^{t+}

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ASL: Patch-Based Super-Resolution

• Similar to the non-local mean denoising method

$$T^{-1} = rac{1}{Z_i} \sum_{j \in V_i} X_j^t \, \omega_{i,j}^t$$

• $\omega_{i,j} \rightarrow$ weights, patch-based similarity in both perfusion and anatomical

$$\omega_{i,j} = \exp - \left(\frac{\|N(X_{i,\text{anat}}) - N(X_{j,\text{anat}})\|_{\mathscr{L}_{2}}^{2}}{\sigma_{i,\text{anat}}^{2}} + \lambda \frac{\|N(X_{i,\text{asl}}) - N(X_{j,\text{asl}})\|_{\mathscr{L}_{2}}^{2}}{\sigma_{i,\text{asl}}^{2}} \right)$$

ω

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ASL: Patch-Based Super-Resolution

• Similar to the non-local mean denoising method

$$X_i^{t+1} = \frac{1}{Z_i} \sum_{j \in V_i} X_j^t \,\omega_{i,j}^t$$

• $\omega_{i,j} \rightarrow$ weights, patch-based similarity in both perfusion and anatomical

$$P_{i,j} = \exp - \left(\frac{\|N(X_{i,anat}) - N(X_{j,anat})\|_{\mathscr{L}_{2}}^{2}}{\sigma_{i,anat}^{2}} + \lambda \frac{\|N(X_{i,asl}) - N(X_{j,asl})\|_{\mathscr{L}_{2}}^{2}}{\sigma_{i,asl}^{2}} \right)$$

$$(N_{i,asl}) = \sum_{i=1}^{N(X_{i,asl})} \frac{|N(X_{i,asl})|}{\sigma_{i,asl}^{2}} + \lambda \frac{|N(X_{i,asl}) - N(X_{i,asl})||_{\mathscr{L}_{2}}^{2}}{\sigma_{i,asl}^{2}} + \lambda \frac{|N(X_{i,asl}) - \lambda \frac{|N(X_{i,asl}) - N(X_{i,asl})||_{\mathscr{L}_{2}}^{2}}{\sigma_{i,asl}^{2}}} + \lambda \frac{|N(X_{i,asl}) - \lambda \frac{|N(X_{i,asl}) - N(X_{i,asl})||_{\mathscr{L}_{2}}^{2}}{\sigma_{i,asl}^{2}}} + \lambda \frac{|N(X_{i,asl}) - \lambda \frac{|N(X_{i,asl}) - N(X_{i,asl})||_{\mathscr{L}_{2}}^{2}}{\sigma_{i,asl}^{2}}} + \lambda \frac{|N(X_{i,asl}) - \lambda \frac{|N(X_{i,asl}) - N(X_{i,asl})||$$

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ASL : Patch-Based Super-Resolution

on simulated data

II Validation





Low resolution







image

Trilinear interpolation

B-splines interpolation

Proposed reconstruction

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ASL : Patch-Based Super-Resolution

on simulated data

II Validation





Low resolution image





Trilinear interpolation

B-splines interpolation

Proposed reconstruction

on clinical data



Structural images

DSC CBF map Low resolution ASL CBF map Super-resolved CBF map

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Detection of Perfusion Abnormalities









- Heteroscedasticity¹ modeling improves the quality of the detections
- New locally multivariate procedure, *a contrario* approach

¹different within-subject variances

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Detection of Perfusion Abnormalities









Heteroscedasticity¹ modeling improves the quality of the detections

• New locally multivariate procedure, a contrario approach

¹different within-subject variances

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Modeling Heteroscedasticity in ASL



 $\widehat{Var}(\hat{\beta}_{patient})$

Bpatient

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Modeling Heteroscedasticity in ASL





General Linear Model

$$\begin{bmatrix} \hat{\beta}_1 \\ \vdots \\ \hat{\beta}_{n-1} \\ \hat{\beta}_n \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ \vdots & \vdots \\ 1 & 0 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} \beta_{controls} \\ \beta_{patient} \end{bmatrix} + \begin{bmatrix} \hat{\gamma}_{G_C}^1 \\ \vdots \\ \hat{\gamma}_{G_C}^{n-1} \\ \hat{\gamma}_{G_C}^n \end{bmatrix}$$

with:

$$\gamma^s_{G_C} \sim \mathcal{N}(0, \ \sigma^2_{G_C} \)$$

Patient







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Modeling Heteroscedasticity in ASL



Two sources of variation are combined : between-subject and within-subject variances

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Modeling Heteroscedasticity in ASL



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Modeling Heteroscedasticity in ASL





- **a** Mean perfusion estimate $\hat{eta}_{controls}$
- D Homoscedastic model : $\hat{\sigma}_{G_{C}}$
- 9 Heteroscedastic model, between-subject : $\hat{\sigma}_G^2$

Heteroscedastic model, within-subject :

d

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Modeling Heteroscedasticity in ASL



Detections of perfusion abnormalities





Ground Truth



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Homoscedastic Heteroscedastic model model

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Resting-State ASL



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Resting-State ASL



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Resting-State ASL



Impact of Acquisition Time in Resting-State ASL

Context

- ASL can be used to study cerebral activity
- $\bullet~$ resting-state functional MRI \rightarrow functional connectivity

- Contribution (Vallée et al., 2020)

Impact of the acquisition time on the quality of the estimated networks

Impact of Acquisition Time in Resting-State ASL

Context

- ASL can be used to study cerebral activity
- $\bullet~$ resting-state functional MRI \rightarrow functional connectivity

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Impact of the acquisition time on the quality of the estimated networks

III Results

Impact of Acquisition Time in Resting-State ASL

Context

- ASL can be used to study cerebral activity
- resting-state functional MRI → functional connectivity

Contribution (Vallée et al., 2020)

Impact of the acquisition time on the quality of the estimated networks





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Neurofeedback

Neurofeedback

 \rightarrow consists in presenting a subject with a stimulus directly related to his/her current brain activity

• can be used to teach subjects to regulate their own brain functions



wikipedia

Perspectives

Neurofeedback: Brain Imaging Modalities

- Electroencephalography (EEG) → main modality used by clinical practitioners, but low spatial resolution
- functional MRI \rightarrow high spatial resolution & possibility to image deep brain structures, but low temporal resolution and high costs/constraints



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- Neurinfo imaging platform : MRI-compatible EEG cap
- Hemisfer Project : collaboration with the Hybrid and Panama Inria teams and involving clinicians
 - hybrid EEG-MRI neurofeedback
 - two clinical studies \rightarrow on stroke and depression patients.



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 - hybrid EEG-MRI neurofeedback
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Context

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Electrodes Detection During Simultaneous EEG/fMRI

- $\bullet~$ EEG source localization \leftrightarrow spatial electrodes position
- Often : approximate, using fiducial points, or external equipment
- Here : MRI = external measurement instrument ?

Context

(i)

Contribution

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Electrodes Detection During Simultaneous EEG/fMRI

- EEG source localization ↔ spatial electrodes position
- Often : approximate, using fiducial points, or external equipment
- Here : MRI = external measurement instrument ?
 - $\bullet~$ But MRI-compatible EEG cap \rightarrow designed to be as invisible as possible on most MRI sequences
 - Ultra-short echo-time (UTE) sequence







Volume Rendering of UTE

ullet ightarrow Deep learning detection step, followed by a registration-based phase

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Electrodes Detection During Simultaneous EEG/fMRI



Machine learning step : 3D U-Net trained on UTE-PETRA (input) sequences and labeled electrodes positions (output)



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Electrodes Detection During Simultaneous EEG/fMRI

Registration-based refinement step

 Iterative Closest Point (ICP) to register intermediate detections to an average EEG cap model



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Electrodes Detection During Simultaneous EEG/fMRI

II Validation

	Deep learning detection	Final results
$\begin{array}{l} \text{Position Error} \\ \text{(mean } \pm \text{std in mm)} \end{array}$	6.78 ± 25.4	2.23 ± 1.4
PPV (%)	96.3	99.8
# Detections	67.7	65
# Labeling Errors mean (max)	3.2 (13)	0 (0)

+ same model (learned on the PETRA sequence) / test on an other UTE sequence \rightarrow worse detections from NN but corrected after ICP

 \rightarrow ICP step brings important robustness (faster machine learning step, different UTE sequences)

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Joint EEG-fMRI Neurofeedback : Source Estimation



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Joint EEG-fMRI Neurofeedback : Source Estimation



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Joint EEG-fMRI Neurofeedback : Source Estimation





- During neurofeedback sessions : real-time constraint \rightarrow no source reconstruction
- What about a posteriori analyses ?
- Ideally : EEG+fMRI \rightarrow high spatial **and** temporal resolution

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Joint EEG-fMRI Neurofeedback : Source Estimation

-☆- Contribution

(Noorzadeh et al., 2017; Oberlin et al., 2015)

Combining EEG and fMRI to spatio-temporal source estimation



- Estimating S is an ill-posed inverse problem in each case
- \rightarrow Joint linear model with sparse constraint

$$\hat{\mathbf{S}} = \arg\min_{\mathbf{S}} \left\{ \alpha \left\| \mathbf{G}\mathbf{S} - \mathbf{E} \right\|_{\mathscr{L}_{2}}^{2} + (1 - \alpha) \left\| \mathbf{S}\mathbf{H} - \mathbf{B} \right\|_{\mathscr{L}_{2}}^{2} + \lambda \left\| \mathbf{S} \right\|_{\mathscr{L}_{1}} \right\}$$

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Joint EEG-fMRI Neurofeedback : Source Estimation

II Validation

8 healthy subjects, right hand motor task, simultaneous EEG-fMRI



 \rightarrow High-resolution temporal reconstruction, but not validated on real data

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Prediction of Neurofeedback Scores from EEG

- Context
- EEG-fMRI joint neurofeedback: promising for brain rehabilitation
- But MRI \rightarrow costly, exhausting, time-consuming
- Hemisfer stroke rehabilitation protocol: alternates between EEG-fMRI and EEG-only sessions
 - Is it possible to enhance EEG-only neurofeedback sessions ? using information from joint EEG-fMRI sessions ?



Cury et al., 2020)

Introduction 00 Arterial Spin Labeling

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Prediction of Neurofeedback Scores from EEG

$$\hat{\boldsymbol{\alpha}} = \arg \min_{\boldsymbol{\alpha}} \left[\sum_{t=1}^{T} \frac{1}{2} \left(\frac{\mathbf{NF}_{\mathbf{fMRI}}(t)}{\mathbf{NF}_{\mathbf{fMRI}}(t)} - \left(\mathbf{X}(t), \boldsymbol{\alpha} \right) \right)^2 + \varphi(\boldsymbol{\alpha}) \right]$$
Actual NF_{fMRI}(t) Predicted NF_{fMRI}(t)

 $\begin{aligned} \text{regularization}: \phi(\boldsymbol{\alpha}) &= \lambda \|\boldsymbol{\alpha}\|_{2,1} + \rho \|\boldsymbol{\alpha}\|_{1} \\ &= \lambda \underbrace{\sum_{m}}_{\text{spatial sparsity frequency smoothness}} \underbrace{\sqrt{\sum_{b} \alpha_{m,b}^{2}}}_{\text{Group sparsity on freq.}} + \rho \underbrace{\sum_{m,b} |\alpha_{m,b}|}_{\text{Group sparsity on freq.}} \end{aligned}$

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Prediction of Neurofeedback Scores from EEG

II Validation





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Prediction of Neurofeedback Scores from EEG



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Arterial Spin Labeling

 Arrival Time can also be estimated but varies across brain → Acquiring for multiple Post-Labeling Delays (PLD)





AAT (Gallichan and Jezzard, 2009)

- → How to choose the PLDs ? how many repetitions for each ? Can Super-Resolution help ?
 - Functional Connectivity \rightarrow ASL vs BOLD ? Links with structural connectivity ?
- → Preliminary results: intrinsic connectivity inside networks (two-by-two voxel correlations)



ASL : Pediatric Applications

- Thanks to its non-invasiveness, ASL is beginning to be used for pediatric applications
- New methodological issues (need for a template of normal, age-related, perfusion changes, effect of sedation)
- early perfusion deficits ↔ abnormal localized brain growth ? possibility to incorporate perfusion information in a computational model of human brain growth ?



(Tallinen et al., 2016)

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Towards a more portable neurofeedback

- Learning from multimodal EEG-fMRI neurofeedback sessions to enhance EEG-only sessions
 - → portability of the model learned outside the MRI scanner: new challenges, dealing with a different number of electrodes, absence of ground truth
 - $\rightarrow\,$ Ideally : assess the response of subjects to the predicted bi-modal NF scores
- Functional near-infrared spectroscopy as an alternative to fMRI ?



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Towards a more personalized multimodal neurofeedback

- Brain Connectivity & Neurofeedback
 - → Does the rehabilitation of stroke patients lead to a spatial reorganization of functional brain networks?
 - → How does this reorganization affect the improvement of clinical signs?
 - \rightarrow Once this reorganization is better understood, how can it be taken into account to propose new NF protocols in order to better adapt them to each patient?
- Multisensory Neurofeedback
- → e.g. Haptic Feedback for motor rehabilitation



Thank you for your attention

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