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Magnetic Resonance for Brain and Spinal Cord imaging and multimodal functional imaging

Elise Bannier

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Mémoire pour l'obtention de
L'HABILITATION À DIRIGER LES RECHERCHES
de l'Université de Rennes 1

Presented by
Elise BANNIER

Magnetic Resonance for Brain and Spinal Cord imaging and multimodal functional imaging

Defense scheduled on January 10th 2023

in front of the following jury

<i>Reviewers:</i>	Michel DOJAT	-	Research Director at INSERM, Grenoble, France
	Laure FOURNIER	-	PU-PH, University Paris Descartes, France
	Ponnada NARAYANA	-	Professor, University of Texas, Houston, USA
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	Isabelle LOUBINOUX	-	Research Director at INSERM, Toulouse, France
	Gilles EDAN	-	PU-PH, University of Rennes, France

Foreword

I was recruited in 2009 as MR Physics research engineer to take part in the creation of the Neurinfo MR facility funded by the a national - federal program (CPER) and the FEDER to install a 3 Tesla research scanner in Rennes. The project involved the University of Rennes 1, the University Hospital of Rennes, the Cancer research center, Inria and Inserm intitutes. It was led by Christian Barillot, head of the Empenn team, to support clinical and methodological research in the field of MRI with a major focus on the Central Nervous System.

I rapidly joined the research dynamic on multiple sclerosis (MS) imaging. In 2010, we had the opportunity to welcome Pr Ponnada Narayana during his sabbatical. Among many other topics, he encouraged us to invest the field of spinal cord imaging for MS and invited us to Houston to discover their facility. We secured funding with the EMISEP study and joined the international effort on spinal cord imaging and image processing led by Julien Cohen-Adad in Montreal. My contributions ranged from sequence optimization to multicenter protocol harmonization to conduct clinical imaging research studies, coordination of data collection, data processing and developing collaborations. In the first chapter of this document, I will focus on the first results of the EMISEP study and related publications. These contributions were achieved in close collaboration with Dr Anne Kerbrat partner from the outset, and Benoit Combés who joined the project a few years later, bringing together clinical, MR physics and image processing expertise.

Beside specific imaging projects, through my position as research engineer at Neurinfo, I got involved in multicenter imaging and data sharing. This resulted in the participation in two white papers which I will present in a dedicated chapter.

In parallel, I invested the field of task based BOLD functional MRI. With clinicians, we designed several tasks to study decision making, emotional prosody, representation in space, 3D vision, working memory, inhibition or memory. Since 2014, we have expanded our field of research to multimodal functional applications with EEG-fMRI and, since 2019, Near Infrared spectroscopy MRI. In the third chapter of this document, I will present a selection of these studies for which I had the opportunity to supervise PhD Students.

Acknowledgments

I would like to thank the committee members for accepting to evaluate this research, as well as my colleagues from the Neurinfo facility, the University Hospital and the Empenn team. I would not be here if it was not for Christian Barillot and Jean-Yves Gauvrit who offered me this position. I am very grateful to them also for their efforts as well as those of Jean-Christophe Ferré, Yves Gandon and Gilles Edan, allowing me to stay on a permanent position at the hospital to develop my research and Ponnada Narayana for guiding us when setting up the facility. I would also like to thank Pierre Maurel and Emmanuel Caruyer for taking over the scientific leadership of Empenn and Neurinfo after Christian's passing and all those who encouraged me to present this HDR, Jacques Felblinger and my Inria mentor Aline Roumy for the insightful discussions and practical advice. I am very grateful to the MR technologists that have (Agnès, Anne, Fabien, Jeanne, Marie-Françoise, Marithé, Mathieu) or still are (Catherine, Gwenola, Lucille, Stéphanie, Vanessa) contributing on a daily basis to acquiring quality data for all the research projects going on at Neurinfo, their enthusiasm and professionalism to support even our most crazy ideas. I have a special thought for Isabelle with whom we have shared the vissitude of Neurinfo since 2009 and for Catherine, unfailing support from the beginning of Neurinfo, who also embarked the adventure of multicenter protocol deployment. Finally, my thanks go to the researchers, clinicians, research engineers or post-docs, I had the pleasure to collaborate with, and the students I had the chance to supervise. They are generally first authors of the works presented here and are credited accordingly.

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1

MR imaging for Multiple Sclerosis: Brain and Spinal Cord

Multiple Sclerosis (MS) is the most prevalent neurodegenerative disease affecting young adults. As of 2020, 2.8 million people suffered from MS worldwide, a majority of which leaving in Northern America, Europe and Australia. Many drugs have been developed in the past decades to slow down disease evolution but multiple sclerosis still cannot be cured.

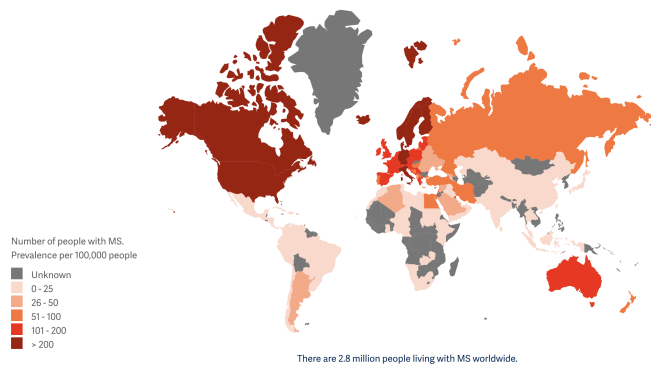



Figure 1: Worldwide MS Prevalence per 100 000 inhabitants as of 2020 from atlasofms.org.

MR imaging is used in clinical routine for MS diagnosis, with or without contrast agent injection. In particular, lesion dissemination in time (DIT) and

dissemination in space (DIS) allow to confirm MS diagnosis [156]. Beyond diagnosis, imaging is also useful to follow disease evolution, detect new or evolving lesions and personalize treatment.

In France, the OFSEP national recommendations advise a yearly MR examination of the brain and a spinal cord MR examination every three years. As a means to organize and structure data collection, improve clinical follow-up and research in the field of MS, the imaging protocol was standardized at the national level in 2015 as part of the OFSEP initiative [42] and updated in 2020 [22] as illustrated in Figure 2.

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2020 OFSEP Protocol	
Brain MRI	Spine MRI
Recommended sequences	
Standard OFSEP protocol	Standard OFSEP protocol
3D unenhanced T1	Sagittal T2
Axial DWI + ADC	Sagittal Gd-enhanced T1 * (1 st diagnosis)
<i>Gd Injection (0.1 mmol/kg) *</i>	
3D FLAIR	
Short OFSEP protocol (PML scrutiny)	
Axial DWI + ADC	
3D FLAIR	
Optional Sequences	
Axial 2D TSE DP/T2 ou 3D T2	Axial T2 GE of the most prominent lesion
DTI ≥ 15 directions	Axial Gd-enhanced T1 *
2D T2 EG or SWI (1st diagnosis)	Sagittal STIR
3D DIR	
3D Gd-enhanced T1 *	
Time-points for injection of gadolinium	
- At initial diagnosis	- [Optional] In case of exacerbations
- If previous MRI is not available	- [Optional] In case of PML suspicion
- Introduction of new DMT	- [Optional] In case of intercurrent diseases
- 6 months after new DMT	
<small>* Macrocyclic agent at the dose of 0.1 mmol per kilogram of body weight</small>	

Fig. 3. The OFSEP MRI protocol. Flyer summarizing the moment to use Gd-based contrast agents and sequences for brain and spine scans under the OFSEP's recommendation.

Figure 2: Reproduced from [22]. 2020 OFSEP protocol recommendations.

These recommendations slightly differ from the european MAGNIMS recommendations illustrated in Figure 3 [156]. The OFSEP protocol pushes for 3D isotropic millimetric sequences in the brain, nowadays more routinely available and better suited for image processing tasks among which lesion segmentation, lesion load measurement or atrophy measurements. In turn, the MAGNIMS protocol gives specific recommendations for optical nerve imaging.

	Multiple sclerosis diagnosis	Assessment of disease activity and monitoring effectiveness of the disease-modifying treatment*	Safety monitoring for disease-modifying treatment (eg, progressive multifocal leukoencephalopathy screening)
Brain MRI protocol			
Axial T2-weighted (TSE or FSE) sequences†	Recommended	Recommended (optional if high-quality sagittal 3D T2-weighted FLAIR and multiplanar reconstruction in axial and sagittal planes are available)	Recommended (optional if high-quality sagittal 3D T2-weighted FLAIR and multiplanar reconstruction in axial and sagittal planes are available)
Sagittal T2-weighted FLAIR (preferably 3D; fat suppression is optional)	Recommended	Recommended	Recommended
Axial T2-weighted FLAIR (unnecessary if a sagittal 3D FLAIR with multiplanar reconstruction is obtained; fat suppression is optional)	Recommended	Recommended	Recommended
Axial (or 3D sagittal) T1-weighted sequences after contrast‡	Recommended	Optional	Optional
Diffusion-weighted imaging	Optional	Optional (should be considered for differential diagnosis)	Recommended
Double inversion recovery or PSIR for detecting cortical or juxtacortical lesions	Optional	Optional	Optional
High-resolution T1-weighted sequences (isotropic 3D acquisition; for quantitative assessment of brain volume)	Optional	Optional	Not required
Susceptibility-weighted imaging	Optional for assessing the central vein sign	Not required	Not required
Optic nerve MRI protocol			
Axial and coronal fat-suppressed T2-weighted sequences or STIR of optic nerve	Optional (can be considered in some clinical situations; 2D or 3D acquisition)	Not required	Not required
Axial and coronal fat-suppressed T1-weighted sequences post contrast of optic nerve	Optional (can be considered in some clinical situations; 2D or 3D acquisition)	Not required	Not required
Spinal cord MRI protocol			
At least two of: sagittal T2-weighted sequences (TSE or FSE), proton density-weighted sequences (TSE or FSE), or STIR	Recommended	Optional	Not required
Sagittal 3D heavily T1-weighted sequences (PSIR or magnetisation-prepared rapid acquisition of gradient echoes) only for the cervical segment	Optional	Optional	Not required
Axial T2-weighted (TSE or FSE) or gradient-recalled echo to corroborate, characterise, and confirm lesions detected on sagittal images or to detect lesions in spinal cord segments with high clinical suspicions of involvement	Optional	Optional	Not required
Sagittal T1-weighted sequences (TSE or FSE) before contrast	Optional	Optional	Not required
Sagittal T1-weighted sequences (TSE or FSE) after contrast‡	Recommended	Optional	Not required
Axial T1-weighted sequences (TSE or FSE) after contrast‡	Optional	Optional	Not required
TSE=turbo spin echo. FSE=fast spin echo. FLAIR=fluid attenuated inversion recovery. PSIR=phase-sensitive inversion recovery. STIR=short tau inversion recovery. *Spinal cord MRI for assessing treatment efficacy and monitoring disease activity is not recommended on a regular basis but is advised for special clinical conditions only. †A dual echo (proton density-weighted and T2-weighted) sequence can be considered as an alternative to a single echo T2-weighted sequence. ‡Standard doses of 0.1 mmol/kg bodyweight, macrocyclic gadolinium chelates only, with a minimum delay of 5–10 min. §One of these sequences could replace T2-weighted sequences, proton density-weighted sequences, or short tau inversion recovery.			
Table 2: Standardised brain, optic nerve, and spinal MRI protocols			

Figure 3: Reproduced from [156]. 2021 MAGNIMS recommendations.

Imaging was historically restricted to the brain because spinal cord imaging was challenging, of unreliable quality and time consuming. With the progress of spinal cord MR imaging [144], it became possible to add spinal cord imaging to clinical routine examinations [157].

Several histological [68] and radiological studies reported in the following review [95] have reported frequent spinal cord focal lesions, in particular in the cervical spine. More recently these results were emphasized by collecting data

worldwide, among which data from our multicenter study, to produce voxel wise lesion frequency maps [48]. Notably, recent works have confirmed that spinal cord lesions, in particular in the cervical spine, could help differential diagnosis, predict a more severe disease course and better explain clinical, in particular motor, symptoms [74]. Besides, several works have evaluated the sensitivity of one or another sequence to detect or delineate focal spinal cord lesions. Even if the gold standard remains Fast Spin Echo imaging (FSE or TSE) [150, 75], other techniques such as Short Tau Inversion Recovery (STIR) [151] have been proposed. Although STIR provides higher contrast between normal appearing cord and lesion, this sequence is prone to flow artefacts. Some years later, Phase Sensitive Inversion Recovery (PSIR) TSE with phase image reconstruction was reported to provide improved lesion sensitivity and boundary depiction [118]. More recently, the 3D version of this sequence has gained attention for cervical spine imaging [103].

In 2011, Rocca et al, performed a multicenter study [126] to investigate the correlation between atrophy and clinical scores, reporting an association between cervical surface area and Expanded Disability Status Score (EDSS) and stability for multicenter studies.

While conventional imaging allows to depict focal lesions or measure atrophy, quantitative MR pulse sequences can be implemented to assess diffuse damage and potentially lesion severity. Among quantitative MRI techniques, Magnetization Transfer Ratio (MTR) and diffusion imaging have shown potential in the context of multiple sclerosis.

In the following sections I will present a selection of my contributions in the field of spinal cord MR imaging for multiple sclerosis published in the last ten years. These contributions are related to the EMISEP National Clinical multicenter Research Study (in French PHRC) funded by the Ministry of Health in 2012, led by Pr. Gilles Edan and sponsored by the University Hospital of Rennes. The first paper deals with the assessment multicenter variability of MTR imaging, the second paper with the comparison of MTR measurements between healthy controls and MS patient at the early stage of the disease and the third paper investigates the correlation between cervical spine lesion location and motor function assessment.

1.1 Quantitative MRI in the spinal cord - EMISEP: genesis and preliminary results in healthy controls

Context

Magnetization Transfer Ratio is a quantitative magnetic resonance imaging technique which consists in applying a non-selective radio frequency pulse, shifted in frequency with respect to the Larmor frequency, which will saturate the bound protons. Due to the interaction between the bound and free protons, the free proton signal is significantly reduced. The magnetisation transfer ratio (MTR) is calculated as the ratio

$$\frac{MT0 - MT1}{MT0} \quad (1)$$

where MT0 is the image acquired without MT pulse and MT1 the image acquired with the MT pulse. Higher values correspond to higher concentrations of complex molecules [159]. The use of this technique has been the subject of several multi-centre studies and recommendations for the homogenisation and robustness of protocols [69, 127].

Several pathological studies in MS have linked MTR to the composition of brain tissue. Thus, a high MTR correlates with a high content of myelin and axons, both in lesions and in normal appearing white matter [153, 131].

This technique has been used at the encephalic level in order to search for prognostic factors of evolution towards disability [3]. Thus, 73 patients (20 CIS, 34 RRMS, 19 SPMS) underwent an initial brain MRI, then at 12 months, with a magnetisation transfer sequence. They were followed clinically for 8 years. The duration of disease progression, initial EDSS, initial T2 lesion volume, fraction of grey matter normalised to intracranial volume, initial mean magnetisation transfer ratio in grey matter, and percentage change at 12 months in mean magnetisation transfer ratio at the lesion level were associated with worsening disability at 8 years. However, the final model explained only 30 percent of the changes in EDSS observed during follow-up, and only 70 percent of patients were correctly classified as stable or worsened when this model was tested in individual cases.

Magnetic transfer imaging has also been applied to the cervical spine in MS patients, demonstrating the feasibility and interest of this technique. A preliminary study investigated, in 14 patients with relapsing-remitting MS,

the correlation between the initial cervical MTR value and EDSS progression at 18 months [29]. A moderate correlation, though not reaching significance, was found. Another study showed not only a reduction in MTR in the cervical medullary grey matter in a population of 18 subjects with relapsing-remitting MS compared to 13 control subjects, but also a correlation between MTR and the degree of disability of the patients measured by EDSS [2]. Later, Zackowski et al. quantified the damage in the different white matter columns of the cervical cord, differentiating between motor and sensory fascicles. They correlated these alterations with quantitative measures of motor strength and vibratory sensitivity, allowing a more precise exploration of the origin of ambulatory disability [160]. This work was extended to other quantitative measurements such as cervical spine atrophy and diffusion metrics in 129 patients confirming the interest of quantitative imaging to study spinal cord damage in MS [109].

These studies were promising, opening perspectives for the understanding of disability in MS.

Contribution

In order to build on these previous works, together with Gilles Edan and Anne Kerbrat, we applied in 2012 for a National Clinical Research project called EMISEP, designed to carry out a longitudinal study on a homogeneous population of Relapsing Remitting Multiple Sclerosis (RRMS) patients, from the first year of the disease (and not heterogeneous in phenotype and age as in the studies published at the time), followed clinically at 5 years (and not two years as in the rare studies published at the time) in order to judge the potential impact of early focal lesions of the spinal cord on physical disability. Alternative sequences such as PSIR was also included to better detect these focal spinal cord lesions. The overall goal was to complement the study of focal spinal cord lesions with the study of more diffuse damage using quantitative MRI techniques and identify biomarkers of disease evolution.

Patient inclusion criteria were

- RRMS patients according to Mac Donald 2010 criteria [149];
- First clinical event in the year;
- More than 9 lesions on brain MRI or/and spinal cord attack with focal lesion on spinal cord MRI;
- EDSS score below 3;
- age between 18 and 40 years old.

Clinical follow up consisted in the evaluation of

- Relapses and treatments;
- Global disability (EDSS, Functional Systems);
- Disability more related to potential spinal cord lesions:
 - Walking performance (25-foot timed-walked test, 6 minutes walking). nine-hole peg test;
 - Sphincter disturbances (QUALIVEEN questionnaire);
 - ASIA score;
 - Force and vibration sensitivity measurement using dynamoters for vibration sensitivity (Vibratron II, Physitemp Instruments LLC, Clifton, New Jersey, USA) and Force (Microfet2, Hoggan Scientific, Salt Lake City, USA).

Eleven centers were involved, with access to 3T research scanners from different vendors at that time: General Electrics (Bordeaux, Clermont-Ferrand, Nancy), Philips (Lyon, Reims, Toulouse) and Siemens (Dijon, Marseille, Montpellier, Paris, Rennes, Strasbourg). The study was designed to include 80 patients, with a brain and spinal cord MRI at baseline, 1, 2, 3 and 5 years and clinical follow up every 6 months. The imaging protocol is described in Table 1.

Table 1: EMISEP imaging protocol

Coverage	Sequence	Purpose
Whole brain	3D T1	Atrophy, lesions
	Ax PD T2	Lesions
	30 dir DWI	Diffuse damage
	3D FLAIR	Lesions
	3D T1 Gd	Active Lesions
Whole spine	Sag T2 TSE	Lesions
	Sag PSIR	Lesions
	Optional: Sag T1 TSE post Gd	Active lesions
Cervical spine	Ax MultiEcho-GRE (MEDIC)	Lesions
	3D IR-GRE (MPRAGE)	Atrophy, CSA
	3D GRE +/- MT	MTR
	Sag. DTI	FA, MD, Tractography

Study design also included the collection of healthy control data in each center at baseline and at 2 years to measure stability of spinal cord imaging.

The Institutional Review Board approval was obtained in January 2014 and is registered on Clinical Trials as NCT02117375. The imaging parameters were normalized across scanners to provide the same field of view, image resolution, signal-to-noise ratio and contrast for conventional sequences. Quantitative sequences were also harmonized to provide comparable values. Some centers running GE scanning did not have the proper setup (spine coil) or were about to change scanners, compromising longitudinal data collection. All in all, seven centers actually included patients: one with a GE scanner included one patient, one center with a Philips scanner included five patients and a majority of patients were included on Siemens Magnetom scanners, whether Verio, Skyra or Prisma.

Results

In order to validate the reproducibility of our quantitative MTR data, we analyzed within-participant, between-participant and between-center variability of MTR measurements from cervical spinal cord in healthy controls. Data from 32 healthy controls, scanned in 4 centers were included in the analysis. Image processing was performed using the Spinal Cord Toolbox [45] and Anima [40]. These results were published in 2019 [38].

Boxplots and jittered scatterplots of mean MTR measurements in the whole cord per vertebral level are presented in Figure 4 and MTR measurements obtained separately for white matter and gray matter in Figure 5.

Given the 3D nature of the sequence, we observe a bias of MTR values across the cord that can be attributed to B0 and B1 inhomogeneities. Unfortunately, correction for these effects requires additional acquisitions which were not included in the present protocol. Since the volumes were all centered on the C5 vertebral level, the values were stable from C4 to C6 drawing the focus of the analysis to this segment. As illustrated in Figure 6, the between-scanner coefficient of variation was estimated as 0.5 percent, the between-session coefficient of variation 2.0 percent, and the between-participant coefficient of variation 1.4 percent. The resulting aggregate coefficient of variation was 2.5 percent. We concluded from this study that we did not find any evidence of differences in variability between scanners (P for equality of scannerwise inter-participant variance = 0.23) allow further analysis of patient versus healthy control data.

A similar approach was applied to the diffusion data. We had opted for a continuous sampling of the spinal cord. Yet, a major challenge there was to cor-

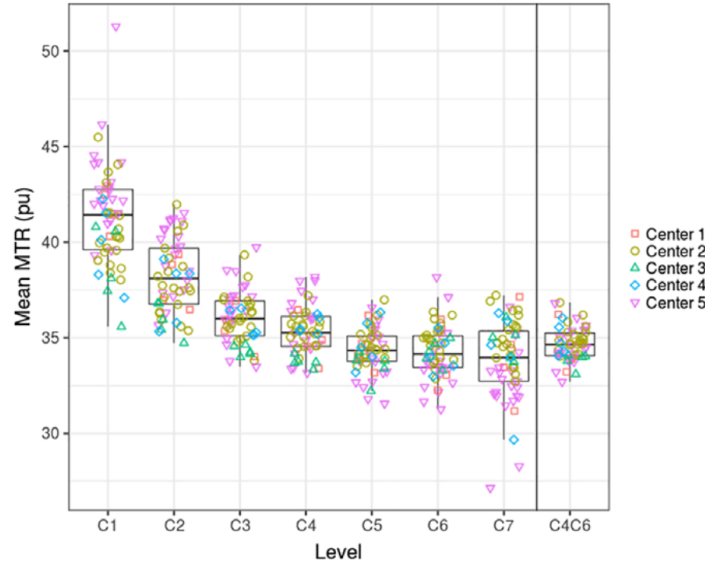


Figure 4: Reproduced from [38]. Boxplots and jittered scatterplots of mean MTR measurements in the whole cord (WC) for vertebral levels between C1 and C7 and for C4-C6.

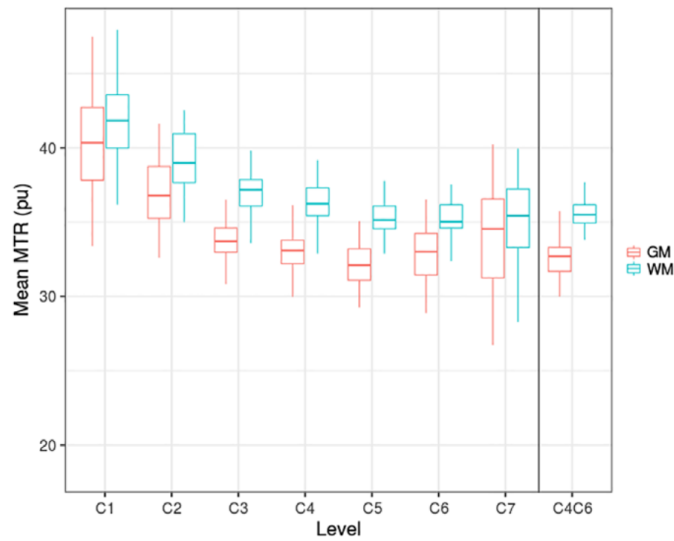


Figure 5: Reproduced from [38]. Boxplots of mean MTR measurements in gray matter (GM) and white matter (WM) for each level between C1 and C7 and for C4-C6.

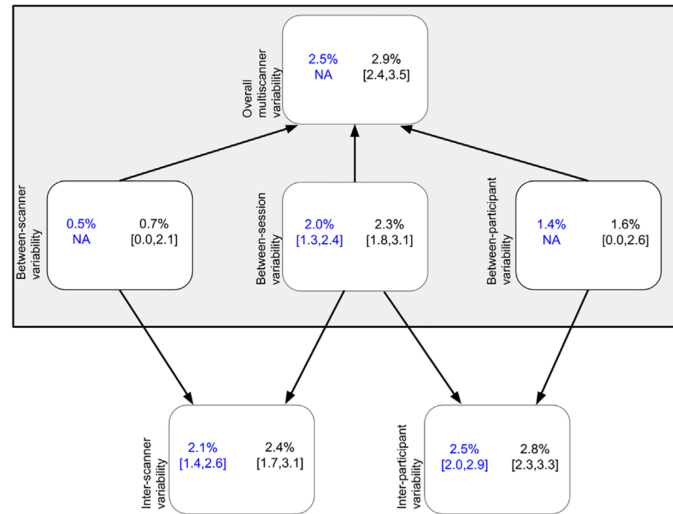


Figure 6: Reproduced from [38]. Coefficients of variation and associated 95% CIs (when available) for the variability estimated using the direct (blue, left) and random-effect (black, right) approaches.

rect for the important distortions related to the sagittal acquisition orientation hence the Head to Foot phase encode direction and the readout EPI sequence. Distortion correction methods were mainly developed for anterior-posterior brain images and had to be adapted for use on sagittal spinal cord data. In [139, 138, 140], different gradient polarity based distortion correction methods were evaluated as illustrated in Figure 7. The corrected diffusion images were compared quantitatively as well as via multi-rater subjective evaluation (submitted).

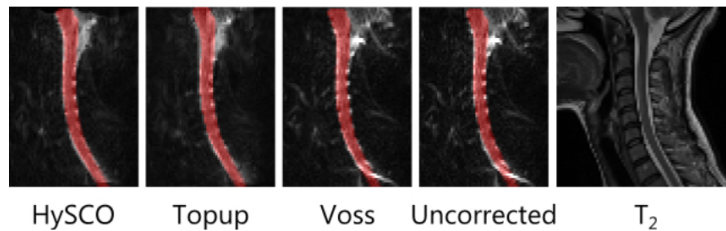


Figure 7: Reproduced from [138]. Example of a corrected $b=0$ volume by each method and T2-weighted rigidly registered.

In [44] the outcome was the quality of the tractography data obtained using deterministic as well as probabilistic approaches, estimating fiber length and number of fibers. Eddy-current, motion effects and susceptibility artefacts correction methods were evaluated. This work allowed to quantify the importance of distortion correction for spinal cord tractography and its impact on tractography rendering, the best result being obtained with a deterministic approach in MRtrix as illustrated in Figure 8.

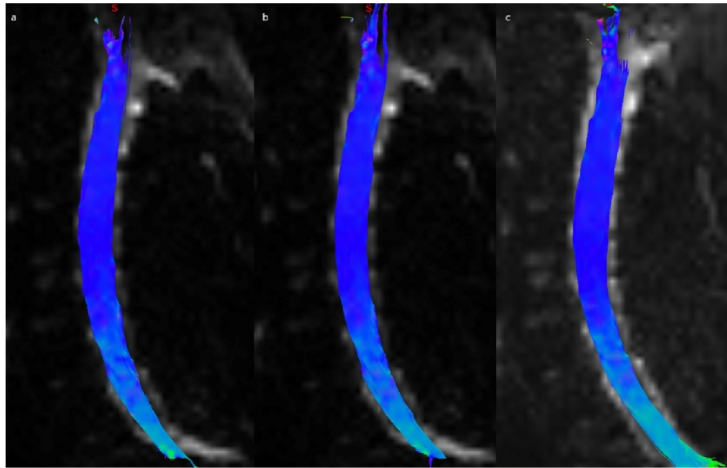


Figure 8: Reproduced from [44]. Example comparison of the tractography rendering before and after artifact corrections, according to the Tensor Det algorithm (deterministic approach in MRtrix). a: Cervical spinal cord tractography before correction, with following features: fiber length: 123.5 mm and number of fibers: 2517. b: Cervical spinal cord tractography after eddy motion correction, with following features: fiber length: 122.9 mm and number of fibers: 2492. c: Cervical spinal cord tractography after Topup correction, with following features: fiber length: 131.5 mm and number of fibers: 2540.

Take-Home Message

- MTR values obtained using scanners from the same manufacturer can be used in multicenter studies without any drastic increase in the variability of the MTR measurements, relative to single-center studies.
- Multicenter diffusion data is less robust and its processing is more prone to analytical variability.
- These results pave the way to the analysis of patient versus healthy control data.

Main related publications: [38, 9, 44, 139, 138, 140]

1.2 Quantitative MRI in the spinal cord - EMISEP: Spinal cord damage in early MS patients

Context

Building on the limited variability of MTR measurement in the cervical spine of healthy controls across centers, we investigated the differences between the group of healthy controls and our sample population of RRMS patients at inclusion. The purpose of this work was threefold: describe lesion distribution in the cervical spine; explore whether MTR metrics are different early in the course of the disease and assess whether MRI metrics can be correlated with clinical scores and used as biomarkers.

Contribution

Data from 60 RRMS patients and 34 healthy controls acquired in five centers was included in the analysis. Spinal cord lesions were identified and manually segmented on sagittal T2 TSE, PSIR and axial MultiEcho-GRE (MEDIC) sequences.

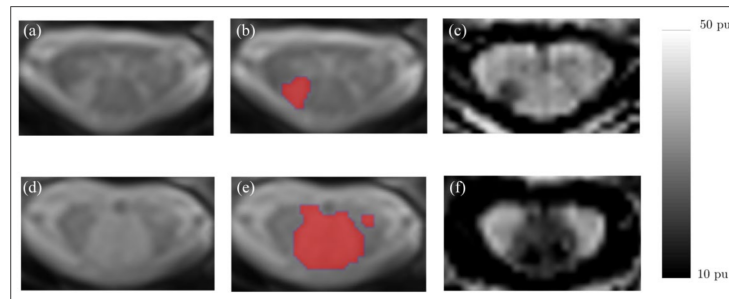


Figure 9: Reproduced from [37]. Axial images of cervical cord lesions. (a)–(d): Hyperintense signal seen on T2*w images; (b)–(e): lesion mask added to T2*w images; (c)–(f): hypointense signal seen on MTR maps; (a)–(c): example of a lesion with mild MTR reduction (mean reduction: 2 pu); (d)–(f): example of lesion with severe MTR reduction (mean reduction: 8 pu).

Brain lesions were automatically segmented, manually checked and corrected when needed. Image processing was done using the SCT and Anima

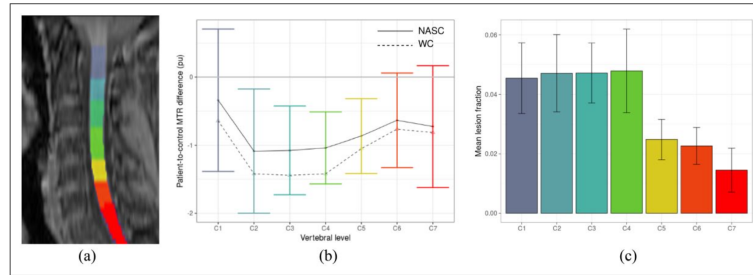


Figure 10: Reproduced from [37]. Mean MTR reduction in NASC and WC for each cervical level. Left to right: (a) example of ROIs extracted from MT0 images; (b) patient-to-control mean MTR reduction (i.e., mean MTR in patients $-$ mean MTR in controls for each ring). Solid lines indicate ML mean MTR reduction in NASC for each vertebral level; (c) mean lesion volume fraction and associated confidence interval at each level for our patient population.

toolboxes [45, 40]. Voxels at the vicinity of lesions (less than 3 voxels) were considered as perilesional areas. MTR metrics in the normal appearing spinal cord and in lesions were computed for each vertebral level and also averaged for the C4-C6 segment. Example of lesions on axial MultiEcho-GRE images and the corresponding lesion segmentation and MTR maps are shown in Figure 9.

Results

As presented in [37], 45 out of 60 patients presented with one or more spinal cord lesion with a mean value of 2.9 ± 2.1 lesions, ranging from 1 to 9 lesions. Lesion load computation per vertebral level elicited higher lesion prevalence between C2 and C5 correlated with mean MTR values per vertebral level as illustrated on Figure 10.

As shown in Figure 11, mean MTR values obtained in patients averaged over levels C4-C6 were significantly different from those obtained in healthy controls. This difference remained when comparing the normal appearing spinal cord (NASC) in patients, i.e., excluding lesions. As expected, mean MTR values in lesions were significantly lower than those measured in the NASC. Interestingly, when dividing patients in 3 groups (0, 1 or 2 lesions, 3 or more lesions), mean MTR values decreased with increasing number of lesions, in the whole cord as well as in the NASC.

Follow-up data of the EMISEP study at 5 years is about to be completed,

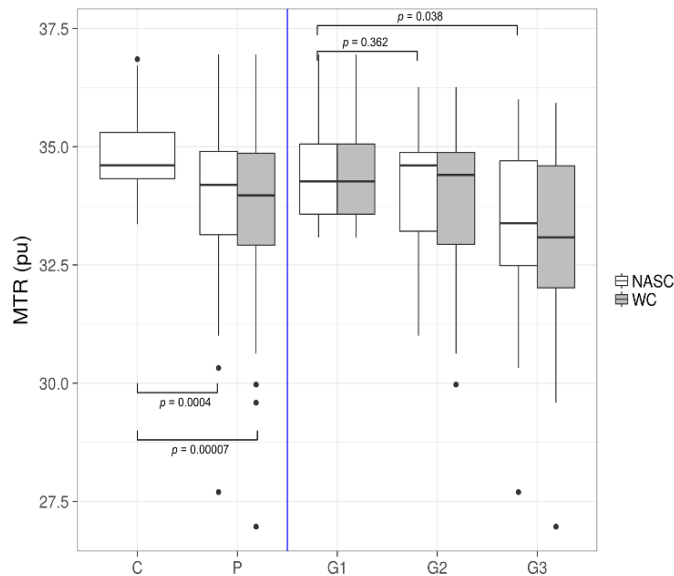


Figure 11: MTR values in whole SC (WC) and normal-appearing SC (NASC). (Left) Mean MTR in controls (in WC) and patients (in NASC and WC), adjusting for the centre effect and (Right) mean MTR in patients NASC as a function of the number of focal lesions

which will allow exploring the evolution of MRI quantitative parameters over time and assess their correlation with clinical evolution.

Discussion

These results bring insights on the focal and diffuse spinal cord impairment at the early stage of MS as well as further research prospects. In particular, automatic lesion segmentation was not available at the time of analysis. This task is tedious, challenging given the small size of the cord and subject to inter-rater variability. Through collaborations with the Neuropoly group in Montreal we contributed to the development of a first tool to automatically segment spinal cord lesions [65] and a broader assessment of lesion frequency maps [48] confirming a privileged localization of MS lesions between C1 and C4 as shown in Figure 12.

As a result of an international effort to gather data from 290 patients, the correlation with clinical scores observed in [48] was further explored in [74].

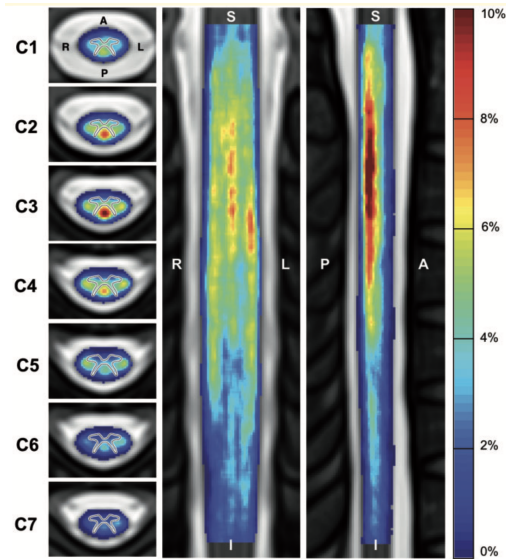


Figure 12: Reproduced from [48]. Frequency of multiple sclerosis lesions in the cervical spinal cord for all patients ($n=642$). Frequency shown in axial (left), coronal (middle) and sagittal (right) view. The axial view shows an average of the lesion frequency across each vertebral level.

These results confirmed the major role of spinal cord lesions, in the CST in particular, and their prognosis value at 2 years.

Take-Home Message

- Cervical spinal cord tissue damage is not restricted to macroscopic lesions in patients with early RRMS and is measurable using MTR
- Lesions are preferentially located in the upper cervical spine
- Spinal cord lesion load is correlated with clinical scores
- Spinal cord lesion load at baseline is a prognosis factor of disease evolution at 2 years.

Main Related Publications: [37, 65, 48, 74, 88, 73]

1.3 EMISEP: Lesion location and motor function

Context

In [123, 124], Rico et al. showed that functional motor scores could be related to functional imaging and that these functional motor scores were affected already at the early stages of MS. The EMISEP imaging protocol did not include functional data. Yet, the brain and cervical spinal cord data already allowed investigating the focal cortico spinal tract (CST) damage and trying to relate it to functional motor scores. An ancillary study was thus designed to investigate the correlation between lesion location on the cortical spinal tract (brain and cervical spine together) and upper limb functional motor scores.

Contribution

In [34], data from 44 RRMS patients from the EMISEP study was analyzed, among which 24 patients also underwent electrophysical evaluations, namely Central Motor Conduction Time (CMCT) using transcranial magnetic stimulation and Triple Stimulation (TST). Data from 17 healthy controls was also used as a reference. Image data processing was performed using the SCT [45] and Anima [40] toolboxes. Spinal cord lesion segmentation was performed manually on the axial MultiEcho-GRE images with the sagittal sequences at hand and brain lesion segmentation was performed using Axial T2-PDw and 3D FLAIR images. Thirty direction diffusion data was processed and registered to the SCT MNI-Poly-AMU template for the spinal cord to extract the left and right CST. Diffusion tractography was computed to extract Fractional Anisotropy (FA), Radial Diffusivity (RD) and Axial Diffusivity (AD). Lesion volume fraction was computed for the whole CST as well as separately for the left and right CST, for the spinal cord and for the brain. FA, RD, and AD values were also computed for each subject for the whole brain, respectively cord as well as in the White Matter (WM), Normal Appearing White Matter (NAWM) and in the lesion masks.

Results

As shown in Figure 13, the presence of a spinal cord lesion largely affects the spinal cord lesion volume fraction. In the brain, as shown in Figure 14 lesion volume fraction is less affected by the presence of a lesion and a lesion can remain silent a while longer.

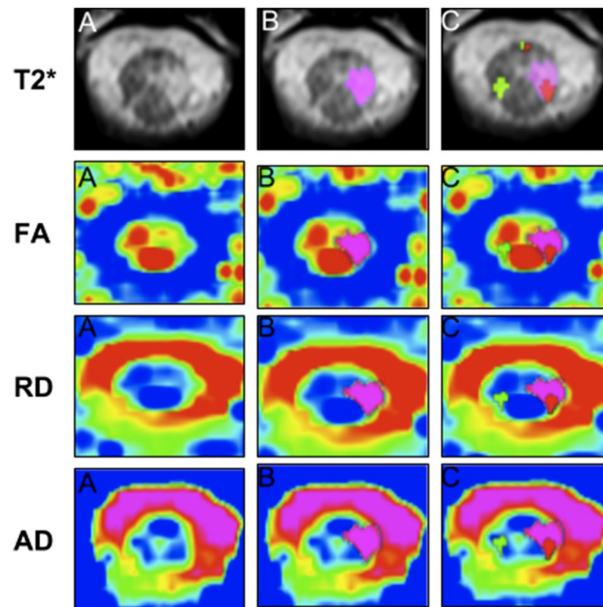


Figure 13: Reproduced from [34]. Example of spinal cord MRI in a patient with RMMS. First row: axial T2*. Other rows: DTI parameter maps. a Native image; b segmented lesion in pink; c masks of corticospinal tract crossing the lesion (left CST in red, right CST in green). FA fractional anisotropy, RD radial diffusivity, AD axial diffusivity).

In our patient population, the number of cervical cord lesions ranged from 0 to 8 (mean 2.5) and from 2 to 71 in the brain (mean 30). Mean lesion fraction were 5.6% in the spinal cord and 0.26% in the brain with a mean lesion volume of 52.5mm^3 and 121.9mm^3 respectively. Six patients had no spinal cord lesion and 2 patients had no CST lesions. Whole spine and CST portion lesion fraction were correlated. Whole brain and CST portion lesion fraction were also, though slightly less, correlated. Spinal cord and brain lesion volume fraction were not correlated.

Diffusion metrics measured in healthy controls and in MS patients are

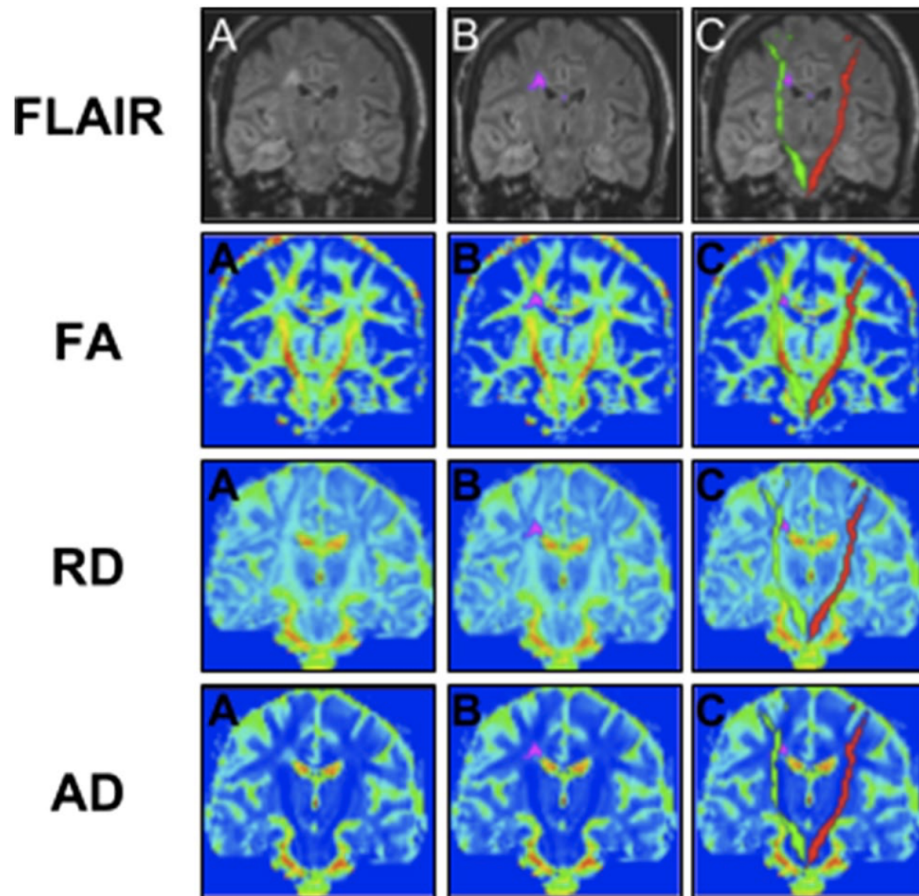


Figure 14: Reproduced from [34]. Example of brain MRI in patient with RRMS. First row: FLAIR acquisition registered on b0 image. Other rows: parametric maps. a Native images, b segmented lesion in pink, c masks of corticospinal tract crossing the lesion (left CST in red, right CST in green), FA fractional anisotropy, RD radial diffusivity, AD axial diffusivity.

presented in Figure 15. FA and RD were significantly different between controls and patients, in the whole cord as well as in the normal appearing spinal cord, i.e., excluding lesions. There were no significant differences in the CST only and in the brain measurements, nor between diffusion metrics and lesion fraction in the spinal cord.

	Controls (spinal cord: <i>n</i> = 18, Brain <i>n</i> = 16)	Patients (<i>n</i> = 43)	<i>p</i> value for no control- to-patient difference
<i>Spinal cord</i>			
FA			
Whole spinal cord	0.719 (0.054)	0.664 (0.079)	0.009
NASC	–	0.661 (0.081)	0.002
CST	0.746 (0.078)	0.712 (0.093)	0.180
Lesion	–	0.655 (0.115)	–
RD (× 1000)			
Whole spinal cord	0.406 (0.076)	0.483 (0.119)	0.014
NASC	–	0.492 (0.127)	0.002
CST	0.366 (0.114)	0.408 (0.138)	0.258
Lesion	–	0.473 (0.149)	–
AD (100×)			
Whole spinal cord	0.158 (0.014)	0.158 (0.014)	0.946
NASC	–	0.159 (0.014)	0.760
CST	0.159 (0.014)	0.158 (0.016)	0.800
Lesion	–	0.156 (0.018)	–
<i>Brain</i>			
FA			
WM	0.346 (0.025)	0.341 (0.020)	0.451
NAWM	0.346 (0.025)	0.342 (0.020)	0.518
CST	0.480 (0.025)	0.469 (0.024)	0.139
Lesion	–	0.311 (0.038)	–
RD (1000×)			
WM	0.610 (0.045)	0.613 (0.046)	0.791
NAWM	0.610 (0.045)	0.611 (0.046)	0.914
CST	0.548 (0.048)	0.556 (0.039)	0.533
Lesion	–	0.870 (0.103)	–
AD (× 100)			
WM	0.105 (0.003)	0.105 (0.004)	0.623
NAWM	0.105 (0.003)	0.104 (0.004)	0.427
CST	0.120 (0.005)	0.120 (0.005)	0.679
Lesion	–	0.139 (0.014)	–

FA fractional anisotropy, RD radial diffusivity, AD axial diffusivity, NA normal appearing

Figure 15: Reproduced from [34], Mean (standard deviation) diffusion parameter values for patients and controls and *p* values associated with no differences between patients and controls

Detailed electrophysiological scores and correlation with clinical scores are presented in [34]. Several correlations were found between CMCT, TST measurements, pyramidal EDSS scores and lesion volume fraction, yet not with diffusion data.

Take-Home Message

- Diffusion metrics show differences between patients and healthy controls, even in the normal appearing cervical spinal cord.
- Functional motor scores are correlated with pyramidal EDSS and lesion volume fraction, yet not with diffusion data.

Main Related Publications: [34]

2

Multicenter imaging and data sharing

MRI is becoming increasingly important in clinical research studies, both in terms of inclusion criteria and endpoints. Markers based on MRI acquisitions are now regularly considered as primary endpoints. Especially in multicenter studies, the management of MRI acquisitions has to take into account the heterogeneity of MRI systems in terms of manufacturers, magnetic fields, coils and software versions. This is due to the number of important parameters that can be specified and optimised to obtain MR images, the variability between the solutions proposed by the manufacturers and the regular technical innovations.

Collecting data from several centers allows to increase sample size, take into account center diversity in terms of equipment and practice and fosters collaborations.

Beyond the level of the multicenter project, data sharing enables achieving unprecedented sample sizes, additional analysis and supports reproducible research, ensuring a most complete and ecological use of the generated data.

Going sideways, I will thus also present recommendation publications I co-authored for multicenter imaging and data sharing.

2.1 Recommendations for multicenter MR imaging

Context

Markers based on the exploitation of imaging data are now used as primary endpoints in clinical research studies. Throughout the deployment of the EMISEP imaging protocol, I collaborated with research engineers from other facilities who were also involved in the deployment of MR imaging protocols related to brain (dementia, traumatic brain injury) or cardiac imaging. One of the first impediment when deploying the imaging protocol was to identify the contact person able to provide us with detailed information on the MR system, the local organisation and to accompany protocol harmonisation. Besides, running an MR research facility requires to obtain and optimise a large number of pulse sequences to answer the needs of the different investigators. This optimisation process requires a lot of testing of different sets of parameters, scanning on healthy controls, sometimes also on patients and data analysis which are, more often than not, not funded by the projects. These scientific exchanges were not covered by the existing societies or infrastructures.

Contribution

To share our experience and efforts on this or another sequence and on study deployment, Irène Troprès (IRMage in Grenoble), Gabriela Hossu (CIC-IT in Nancy), Marie Chupin (CATI in Paris), Jean-Luc Anton (Centre IRMf-INT, CERIMED, Marseille) and myself decided in 2016 to create a network for multicenter MRI mutual aid that was named REMI (Réseau d'entraide multicentrique en IRM). The network was designed to involve MR technicians, research engineers in MR physics or image processing, clinical research assistants as well as researchers in MR physics, radiologists or clinicians with particular interest in MR imaging. To facilitate exchanges and involve MR technicians and clinical research assistants, french language was preferred. France Life Imaging provided financial support to develop the network, funding a project manager for a year, the development of a collaborative tool and catering during gatherings. The initiative was also encouraged by the French Society for MR Physics and Biology in Medicine (SFRMBM) and the medical college for radiology teaching (CERF) through the Force-I task force. We organized meetings 2 or 3 times a year, gathering 40 to 50 people each time, in Paris or switching to virtual meetings during the pandemic. The meeting agendas cover organisa-

tional, regulatory and scientific topics, with presentations from experts in the field as well as round table discussions. All meeting minutes and presentations can be found on our collaborative tool (<https://remi.network/>). Registration is free but restricted to academic members.



Figure 16: Adapted from [67]. MR imaging project actors.

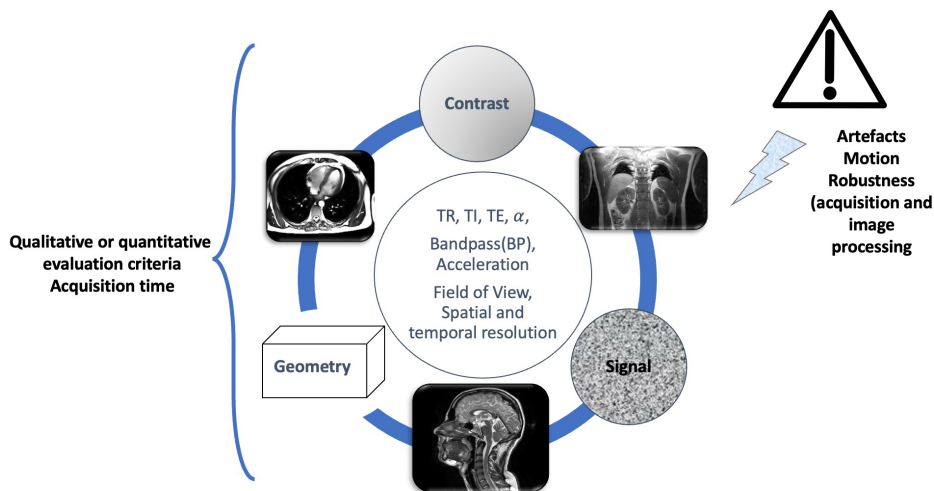


Figure 17: Adapted from [67]. MR imaging protocol optimisation.

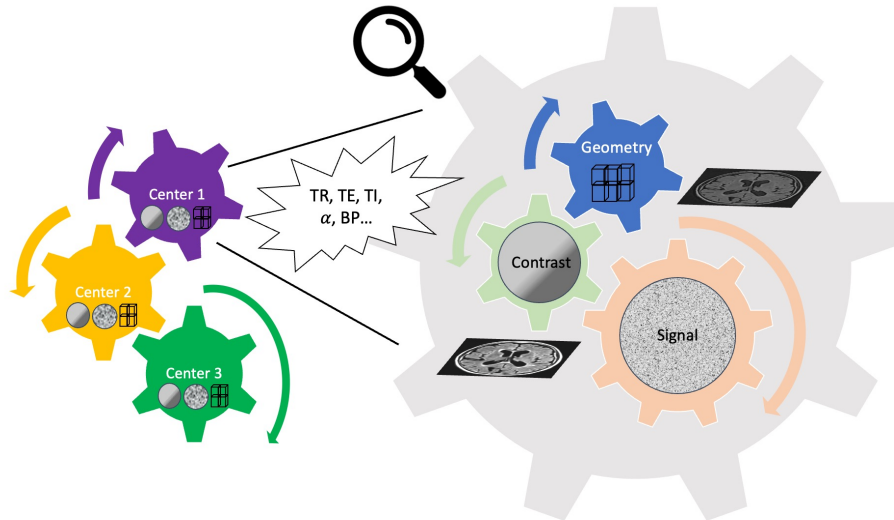


Figure 18: Adapted from [67]. MR imaging protocol harmonisation across centers.

Results

To share the results of the discussions related to multicenter imaging, we decided to write a white paper detailing the steps and the people to involve in order to carry out a multicenter MRI study. Based on the experience and expertise of the members of the REMI, we propose detailed recommendations to the French-speaking community, in order to better take into account the specificities of MRI at all stages of the study and to participate in improving the quality of MRI research. These recommendations also take into account the specificities of MRI research platforms and clinical imaging services, as well as french regulatory constraints at the time of publication [67].

A first chapter presents the regulatory context and the actors (Figure 16).

A second chapter gives recommendations to design the imaging protocol, optimise the imaging protocol, ensure multicenter technical and financial, feasibility as well as data collection as illustrated in Figure 17 and Figure 18.

A third chapter describes protocol deployment steps and a fourth chapter gives guidelines to conduct the study (data collection tracing, quality check, preferably along with the flow and analysis).

Take-Home Message

- Markers based on the exploitation of MRI acquisitions are now used as primary endpoints in clinical evaluation criteria in clinical research studies.
- In multicenter studies, the management of MRI acquisitions must consider the heterogeneity of MRI systems in terms of manufacturers, magnetic fields, coils and software versions.
- All actors must be involved from the beginning of the project.
- In addition to the definition of the MRI protocol and its feasibility in multi-center, the identification of the necessary material and human resources, as well as the associated cost, the collection of data, the control of their conformity, the processing and the analysis of the data, must be considered.

Main Related Publication and communications: [67], Teaching for the French Clinical Research in Imaging Network (F-Crin) and the Diplôme Universitaire for MR Technicians in Clinical Research (MERC)

2.2 Data sharing and the Open Brain Consent Initiative

Context

The time when imaging data was collected and stored on CDs is long gone. Several server applications have been developed to collect and structure data for clinical (Picture Archiving and Communication Systems - PACS) and also for research purposes.

Imaging data can thus be exchanged within the hospital, processed and under specific conditions, i.e., Research context and Privacy Impact Assessment analysis, also transferred outside of the hospital network as illustrated in Figure 19.

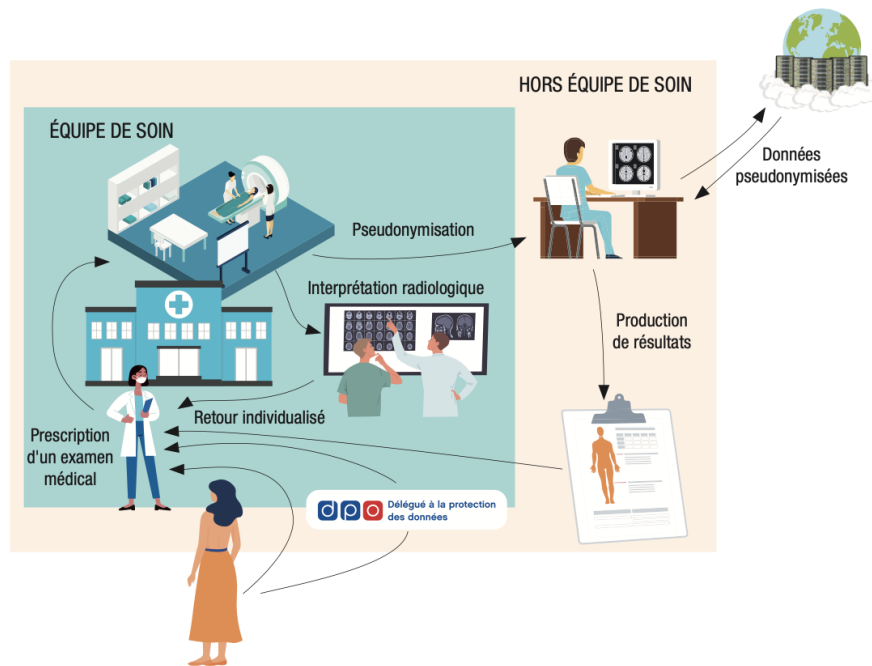


Figure 19: Reproduced from [10]. Imaging data journey - Clinical and research perspective.

Some image managing platforms are based on an ontology in order to allow subsequent searches for specific subject (disease, age range, gender) or data

parameters (acquisition type - Pulse sequence in the case of MR, acquisition parameters, image resolution, ...).

These applications deal with data pseudonymisation (removing all information allowing direct subject identification such as name, address and date of birth) and, when applicable, study timepoint identification. Some of them perform data check to make sure all acquisitions are present, named correctly and complete (number of volumes), online or remotely. Image content quality check is difficult to automatize, often performed manually remotely and a quality check report or a query is sent to the data provider. Besides, image quality criteria are not absolute as they depend in the project goal and the sample population (compliant healthy adults, children or other more or less compliant participants).

The pharmaceutical companies have servers of their own or their instance of a given proprietary application.

Academic open-source solution also exist, one of the most famous worldwide being XNAT (<https://xnat.org/>). Based on the OntoNeurolog project, a software first named InriaNeuroTK was developed by Inria in the 2010's and later renamed Shanoir (standing for SHARING NeuroIMaging Resources) [12]. Other initiatives such as CATIDB [97] and Archimed [102] were developed by the CATI and the CIC-IT Nancy respectively. All three platforms are supported by laboratory fundings and have also been partly supported by the France Life Imaging Transversal Node Information Analysis and Management (FLI IAM) node (<https://www.fli.ai/>).

Contribution

The Empenn team is particularly involved in the development of the Shanoir platform, with operational and research development perspectives. A consortium supported by Inria and FLI-IAM was recently funded to pursue the development of Shanoir, taking into account in the development roadmap the insights of the consortium members, i.e., Shanoir users among which Neurinfo, as well as research perspectives brought by Empenn and FLI-IAM research interests.

As indicated in its name, Shanoir (standing for SHARING NeuroIMaging Resources) was designed to allow data sharing. Conducting an MR imaging study requires gathering fundings in the order several tens of thousands of euros, often from public funding sources. Institutional Review Board (IRB) Approvals are obtained for specific objectives and evaluation criteria. Project

leaders are encouraged to further share their data, for transparency reasons (reproducible research) or to go beyond the initial objectives, pool it with other datasets, address additional related research questions and catalyze research in the field [117]

In Europe, since 2016 and its application in 2018, data sharing is governed by the GDPR regulation (<https://gdpr-info.eu/>). It differs from the so-called "open data" practice which is common in the United States but does not prevent from sharing imaging data as long as the GDPR regulations are respected. The Open Brain Consent Initiative took hold of this question, involving international legal experts and researchers, with a specific focus on brain imaging and European Union regulation. MR brain images in particular allow to reconstruct the face of the participant and face removal algorithms have been proposed to prevent direct identification. These algorithms may bias further processing with tools developed on non defaced data and should be used with caution. Besides, an imaging dataset is a highly complex dataset, composed of millions of voxels with millimetric resolution. The shape of a cerebral gyrus or sulcus, a individual particularity or the presence of lesions may contribute to subject identification, from the sole dataset or by combining this dataset with other publicly available datasets. We must also consider what is possible today and what may become possible in the future, in terms or methods and resources. All-in-all, brain imaging data is personal health - hence sensitive - data and most likely not to be considered anonymous according to the CNIL regulations.

Results

These discussions resulted in the proposition of a two-fold procedure, considering on the one-hand the rights of the data subject and on the other-hand the data controller/processor obligations. Together with Camille Maumet, researcher in neuroinformatics at Inria, and Anne Hespel, Data Protection Officer at the CHU of Rennes, we contributed to these discussions and to the French proposal in particular [8].

The consent form informs the participant of the study rationale, the study design, the objectives and the participant's right as regards to the data. In particular, according to the GDPR, data privacy and usage control are described. Consent is collected for the sole study and subsequently yet separately for potential data reuse.

The data user agreement (DUA) individually commits the person down-

loading the data to not redistribute it nor by any means to try to identify the study participants. This person becomes data controller and is responsible for the appropriate usage of the downloaded data.

These proposals need to be disseminated, adopted by researchers when designing a study and applying for IRB approval and also accepted by patients and healthy controls taking part in imaging studies. With these aims in mind, a book was elaborated by the CNRS to synthesize technological developments in imaging in the recent years and, together with Anne Hespel and Camille Maumet, we were invited to address the ethical and social considerations of the new imaging developments [10].

Discussion

Besides regulatory aspects, the technical accessibility of data must also be improved, according to the FAIR principles: Findable, Accessible, Interoperable and Reusable (<https://www.go-fair.org/fair-principles/>). We started implementing the Data User Agreement in the Shanoir software interface, deriving the template proposed via the Open brain consent initiative to the individual projects, in particular detailing funding sources and reference papers for citation. Thus, any Shanoir registered user accessing a study for which a DUA is uploaded will have to accept the conditions of this DUA. The broadest use to date is the MICCAI MS segmentation Challenge dataset (<https://portal.fli-iam.irisa.fr/msseg-2/>) [39].

Finally, in order to be reusable, data also needs to be sufficiently structured to allow searches and sufficiently described (sequences and parameters used, population description and potential recruitment bias, instructions given to the participant, task description if any among other specifics).

Take-Home Message

- Structured data collection ensures data use and reuse
- Pseudonymized imaging data falls under the GDPR regulation but can be shared with appropriate processes
- Data collection and sharing intentions need to be defined ahead of Institutional Review Board application, included in the participant consent form and in the Data Management Plan

Main Related Publications: [12, 8, 10]

3

Functional MRI

Since the early 1990s, Blood Oxygen Level Dependent (BOLD) functional MRI provides an avenue to explore the healthy or pathological brain function. It reflects the neurovascular coupling inherent to brain activation, namely perfusion, oxyhemoglobin and deoxyhemoglobin concentration changes and relies on the sensitivity of echo planar imaging sequences to the variations of oxyhemoglobin and deoxyhemoglobin concentrations. This results in a so-called hemodynamic response function (HRF), which is convolved with the sequence of stimuli per condition to form the design matrix.

These approaches are complementary to resting-state functional imaging and diffusion imaging approaches that allow the study of structural and functional connectivity of the whole brain, during rest.

The practical advantages of resting state are that task design is unnecessary (conditions, timing), subject compliance is easier to obtain (no instructions but to lie still, with eyes open or closed, yet without sleeping), no specific hardware to supply the stimuli and record subject responses (auditory or visual pathways, response buttons) and yet a wide range of analysis can be performed to investigate functional connectivity alone or in combination with other modalities. Task-based fMRI remains interesting in as much as it allows to investigate specific neural processes performed on demand (language, motor, decision-making, memory, ...), provide additional insights to neuropsychology or neuroscience behavioral task studies and is easier to interpret at the individual level.

In the following sections, I will present a selection of task-based fMRI studies conducted at Neurinfo and for which I co-supervised PhD Students. The first study investigates representation in space in healthy adults and impairment after stroke. The second study deals with developmental fMRI imaging,

investigating the link between in-utero exposition to solvents and organophosphate insecticides and brain function between 10 and 12 years old in a group of healthy children.

3.1 Spatial cognition impairment after stroke

Context

Task-based functional MRI allows to highlight the cerebral areas involved in the performance of a specific task. It can allow a better understanding of brain function in healthy subjects as well as in a pathological context of stroke to evaluate the damage or to study brain plasticity during a rehabilitation program.

Stroke is one of the leading causes of long-term adult disability worldwide [107]. Post-stroke rehabilitation is crucial for long-term patient recovery. In particular, balance disorders lead to an increased risk of falls and impaired autonomy. These balance disorders are related to spatial cognition perception impairment, in particular in the case of right hemispheric stroke. However, the mechanisms underlying spatial perception of the body in space and the way rehabilitation programs stimulating these mechanisms after stroke contribute to brain plasticity and recovery are not completely understood. Prism adaptation and muscle vibrations have been proposed and have shown positive results in patients presenting spatial neglect, i.e. blind to a part of their visual field. Bottom-up approaches manipulating sensorial or visual abilities can directly influence spatial cognition without soliciting subject's consciousness and hence facilitating its application in patients in need [71, 27, ?].

Contribution

The multicenter AVCPOSTIM Study (NCT01677091) led by Pr. Isabelle Bonnan was funded in 2012 by the National Ministry of Health to investigate the effect of a 14 days sensory stimulation program involving neck muscle vibration (NMV) and prismatic adaptation (PA), after a right hemispheric stroke on spatial cognition impairment. Participants were randomized into 4 groups, namely NMV alone, PA alone, NMV and PA, or sham. Eighty seven patients were included. Outcome measures were the subjective perception of straight ahead (SSA), subjective longitudinal body axis (SLB) and weight bearing asymmetry. Eight centers included patients and standardised MRI clinical scans were collected using Shanoir.

A monocentric ancillary study was also funded to investigate using task based fMRI the neural mechanisms underlying SSA and SLB perception as well as the effect of neck muscle vibration while performing these tasks. The

SSA task was adapted from [152] and the SLB task was created for the purpose of this study. Both tasks were implemented using E-Prime v.2.0 (Psychology Software Tools, Pittsburgh, PA, USA) and presented with the Nordic Neurolab Solution (Nordic Neurolab, Bergen, Norway) after creating the stimuli using Blender [41]. Seventeen healthy controls were included in this ancillary study to assess the task which was then presented to patients. Neck muscle vibration was performed outside MRI using the Vibramoov system (Technoconcept, Manosque, France) and in the MRI using a pneumatic prototype system developed on purpose by the same company and compatible with MRI. Both tasks followed a bloc-design with 6 alternating phases of task and control task. As illustrated below, in the SSA task adapted from [152], a vertical bar would move sideways at a speed of 2 degrees per second, between -7 and 7 degrees, from left to right and right to left. Participants were instructed to press the response button each time they perceived the bar crossed their straight ahead plane in the task phase, and each time the bar would change direction in the control phase. In the SLB task, the bar would rotate around the navel at the same speed, between -30 and 30 degrees. Participants were instructed to press the response button each time they perceived the bar would cross their longitudinal body plane in the task phase, and each time the bar would change direction in the control phase. Since the bar was continuously moving, these tasks were not designed to measure spatial deviation but to elicit the brain areas involved in SSA and SLB perception respectively.



Figure 20: Stimuli from the SSA task under fMRI

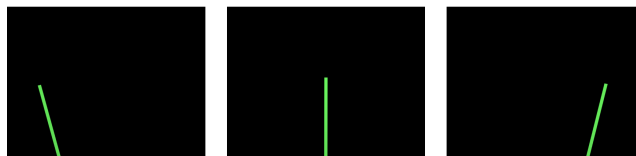


Figure 21: Stimuli from the SLB task under fMRI

Seventeen healthy controls and 14 patients were included in this ancillary study between 2012 and 2017. All participants underwent an fmri scan with

the imaging protocol presented in Table 2.

Sequence	Task
anat 3D T1	
fmri	vibration
fmri	SSA
fmri	SLB
fmri	SSA + vibration
fmri	SLB + vibration

Table 2: AVCPOSTIM fmri protocol

Image processing was performed using SPM12 and Matlab and the automri12 pipeline developed at Empenn.

Results

The results of the clinical RCT AVCPOSTIM study have been submitted for publication but are not yet published.

The results obtained in healthy controls for the SSA and SLB tasks were published in [89]. As illustrated in Figure 22 SSA activations were located in the right parietal lobe, the right lateral occipital cortex, the left lateral occipital cortex, the left parietal lobe and the right frontal lobe. SLB activations were also predominantly located in the right parietal lobe, the right lateral occipital cortex the right frontal lobe and the left lateral occipital cortex but also in the left frontal lobe, the left parietal lobe and the right insula. The differences in activation location between both tasks suggested greater complexity of the SLB task.

During vibration, broader activation clusters were obtained for the SSA task as illustrated in Figure 23 but not for the SLB task.

In patients, activations as well as lesion extent were heterogeneous. These results are still under investigation (Master Thesis). Given the limited number of participants, our observations remain exploratory.

Discussion

There is currently no consensus on the rehabilitation of spatial cognition. This impairment is not always identified and not specifically taken care of. Some

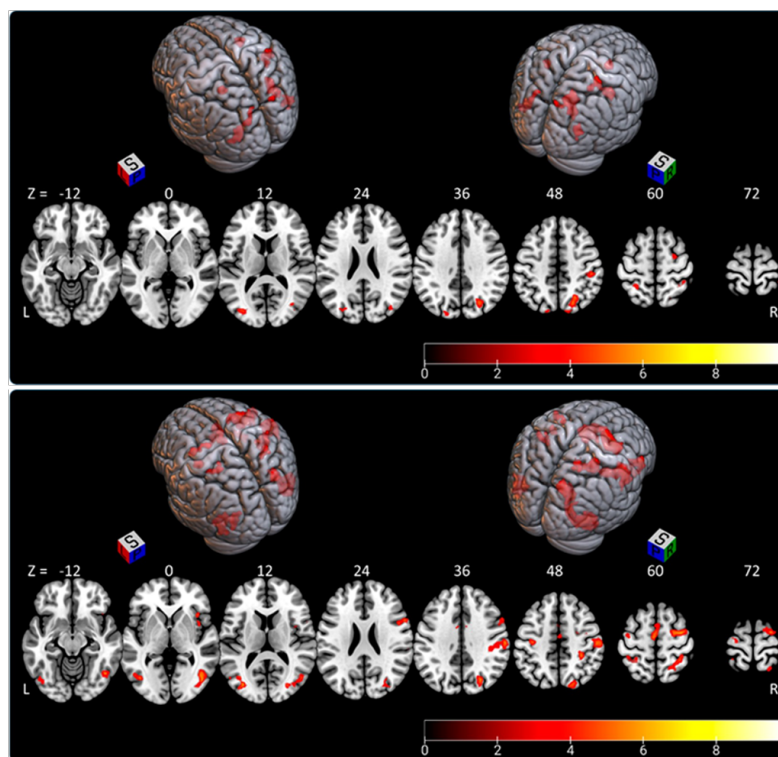


Figure 22: Reproduced from [89] - SSA (top) and SBL (bottom) activations.

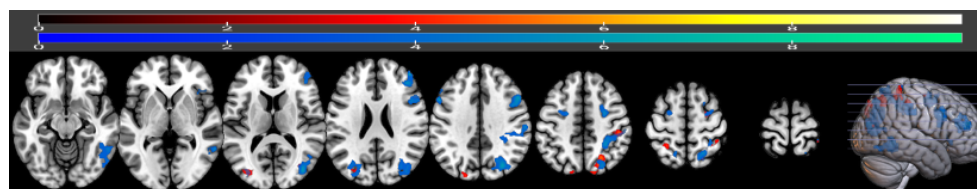


Figure 23: SSA activations under vibration.

patients can present a deviation to the SSA test and not to the SLB test and vice versa. The goal of the MRI study was to investigate the neural underpinnings, assess rehabilitation techniques and improve our understanding of spatial cognition, relating lesion localisation and lesion extension to clinical scores. This fMRI data is unique and deserves further processing such as the investigation taking into account the specificities of stroke patients among which lesion extent, structural damage and modified response function. It also has limitations, among which the limited sample and the bloc-design paradigm. Another hurdle for future stroke fMRI studies is the absence of automated tool for sub-acute and chronic stroke lesion segmentation. This segmentation is tedious and prone to inter-rater variability. This is a topic we investigated in collaboration with Pixyl during Stéphanie Leplaideur's PhD, unfortunately without any satisfying results. We will further investigate this issue in collaboration with Francesca Galassi, assistant professor specialized in machine learning, starting with an ongoing internship.

Take-Home Message

- Both spatial cognition tasks involve a right fronto-parietal network, yet SLB recruits additional brain regions.
- Activations observed with and without vibration are co-localized but activation extension varies.

Main Related Publication: [89]

3.2 Prenatal exposure and teenage fMRI

Context

The increasing prevalence of asthma, obesity, language, hyperactivity and attention troubles in children raises particular concern. Evidence exists that neurotoxicant exposure shares responsibility in the appearance of these troubles [63].

The Inserm PELAGIE Cohort (<https://www.pelagie-inserm.fr/>) is dedicated to investigating the effect of prenatal exposure to solvent and organophosphate insecticides on child development and health. Between 2002 and 2006, 3421 pregnant women living in Brittany were included in the study. Brittany being a semi-rural environment, exposition was related to working as well as home environment. The children were followed during their development and environmental as well as health condition data were collected as described in [56].

Biological samples (hair, blood among others) as well as samples taken at home together with answers to questionnaires were collected during pregnancy, at birth and the children followed after birth.

Contribution

Together with Fabienne Pelé we applied for a grant to investigate the potential effect of prenatal exposure on brain development via imaging. The PERINE project was funded by the Fondation de France in 2014 (NCT02125110). A subset of 101 families took part in this study. Children were all born at term (delivery after 35 weeks of amenorrhea), presenting no major condition at birth (neonatal hospitalization, hypoglycemia, 5 minute-Apgar score <7) nor prenatal exposure to tobacco, alcohol or medical treatment during childhood which could affect their neurodevelopment (methylphenidate, psychotropic or antiepileptic drugs, etc.)

Children were aged between 10 and 12 years old and the imaging protocol adapted accordingly not to exceed 30 minutes MR scan. Anatomical, diffusion, perfusion and task-based fMRI sequences were included.

Among executive functions, inhibitory control is critical for learning abilities [11] and difficulties in the ability to control impulses and to inhibit a prepotent response are related to various pathology such as Attention Deficit



Figure 24: PELAGIE Follow-up Timeline.

Hyperactivity Disorder [158] and poor academic performance. In healthy subjects, Inhibition efficiency during childhood is a strong predictor of future academic and professional outcomes [104]. Notably, memory and inhibition control impairment had been reported in adults at higher exposition [145].

Because of these previous results and because inhibition appears critical in child development, we implemented the inhibition Go/No-Go task in our study. The Go-NoGo task was adapted from [106] for use in children as in [122]. Classically the subjects had to press a button for the Go condition and inhibit their response for NoGo. Green and red smileys were successively presented on a screen. Children were asked to press a button with their right thumb as quickly as possible when seeing a green smiley, but had to refrain otherwise. The task was split in two runs of 5 minutes each. Each run consisted of 150 trials and four 10-second resting periods. A trial was the consecutive presentation of a smiley (duration of 200 ms) and a cross fixation point (duration of 1300 ms). A response was allowed until the next trial began, giving a constant inter-stimulus interval (ISI) of 1500 ms. Smileys appeared in a pseudo-random order: trials at the beginning of runs or following resting periods had to be Go cues, Go cues had to occur at least at three in a row and No-Go cues had to occur individually or at two in a row. The ratio of No-go cues (red smileys) over Go cues (green smileys) was 1:4, in order to elicit a dominant response. The task was implemented using E-Prime v.2.0 (Psychology Software Tools, Pittsburgh, PA, USA) and presented with the Nordic Neurolab Solution (Nordic Neurolab, Bergen, Norway).

Functional MRI studies using such a task evidenced activation of a mainly right-lateralized network including the right middle/inferior frontal gyrus, right inferior parietal regions, and the medial part of the superior frontal gyrus for the NoGo contrast [136]. According to [94, 21], other regions such anterior cingulate cortex are also involved in cognitive control .

The functional and structural data were preprocessed and analyzed using SPM12 in MATLAB. A customized template was created based on the GM

segmentations using a diffeomorphic method known as DARTEL [5]. Hemodynamic response was modeled from child’s answers to cues (correct Go and No-Go cue answers, commission errors, i.e., incorrect answers at No-Go cues), implicit baseline (resting periods, time between trials and incorrect Go answers, i.e., omission errors which were negligible) using a canonical hemodynamic response function (HRF) and its temporal derivative. Functional MRI results were compared to neuropsychological results from the NEPSY [83].

Results

Exploring the correlation between exposure and activations during the Go-NoGo task was the focus of Anne-Claire Binter’s PhD thesis.

Children were mainly girls (56.63%) and aged of 10.8 ± 0.3 in average. They performed the Go/No-Go task with a response latency of 414 ± 87 ms. The commission rate (25.9 ± 13.3 %) was much higher than the omission one (3.3 ± 5 %). Children scores for visual attention scores went from 12 to 30 with a mean value of 21, whereas auditory scores went from 91 to 132 with a mean value of 119.

“Successful No-Go cues” contrast showed activations in regions involved in motor inhibition (bilateral frontal, cingular and insular cortices) and attention (right parietal and temporal gyri). We also observed cerebral activities in motor regions (left pre/post-central region, bilateral anterior cerebellum) and visual regions (right occipital area). For “Successful No-Go versus successful Go” contrast, we obtained increased neural activity in inhibition regions (left insular, right frontal and bilateral cingular cortices) and attention network, including visual attention (bilateral occipital, right inferior parietal and temporal gyri).

These results were in agreement with the literature and activated clusters were further compared with exposition metrics.

In [18], we reported that higher maternal urinary concentrations of two of these ethers were associated with poorer child performance. When children succeeded to inhibit, high ethoxyethoxyacetic acid (EEAA) and moderate phenoxyacetic acid (PhAA) levels were associated with differential activity in frontal cortex, involved in inhibition network.

In [16], moderate levels of organophosphate pesticides were associated with a decreased commission rate, indicating improved performance. Increasing levels of dimethylphosphate and diethylphosphate were associated with decreased brain activity in the left inferior and bilateral superior frontal regions during

Metabolite concentrations (in µg/L)	Performances	Brain activity	
		Inhibition network	Others brain regions
MAA Low: < 52.4 Moderate: [52.4–82.9] High: ≥ 82.9	Ref.	Ref.	↗ R precuneus
EAA Low: < 9.7 Moderate: [9.7–22] High: ≥ 22	Ref.	Ref.	↗ L cuneus
EEAA Low: < 19.8 Moderate: [19.8–86.5] High: ≥ 86.5	Ref. ↘ reaction time	Ref. ↘ med frontal	↘ L temporal
BAA Low: < 19.7 Moderate: [19.7–47.1] High: ≥ 47.1	Ref. ↗ reaction time, ↘ PS score ↘ PS score	Ref.	
PhAA Low: < 146.4 Moderate: [146.4–498.1] High: ≥ 498.1	Ref.	Ref. ↗ R inferior frontal	
2-MPA Low: < 13.2 Moderate: [13.2–24.1] High: ≥ 24.1	Ref.	Ref.	

Figure 25: Reproduced from [18] - Go-NoGo activations in relation with exposition to glycol ethers

successful inhibition. We did not observe any differential activation related to inhibitory demands.

Metabolite levels	N	Right frontal region	ext.	Left frontal region	ext.	Anterior cingular region	ext.	Other brain regions	ext.
		β (95% CI)		β (95% CI)		β (95% CI)		β (95% CI)	
DAP									
Low levels	31	Ref.		Ref.		Ref.		Ref.	
Moderate levels	28								
High levels	31								
DM									
Low levels	38	Ref.		Ref.		Ref.		Ref.	
Moderate levels	25								
High levels	27			-1.2 (-1.6; -0.8)	465				
DE									
Low levels	32	Ref.		Ref.		Ref.		Ref.	
Moderate levels	29	-1.8 (-2.5; -1.1)	1072	-1.7 (-2.4; -1.0)	951				
High levels	29	-1.6 (-2.0; -1.2)	390						

Note: DAP: Dialkylphosphate, DE: diethylphosphate, DM: dimethylphosphate, ext.: cluster extension, Ref.: reference.

β (95% CI): estimated coefficient [95% confidence interval]. Empty cell: no statistically significant difference reported in this region.

Estimates are provided for clusters presented in Fig. 3. All estimates are from mixed-effect generalized linear regression models adjusted for maternal fruit/vegetable consumption (<3 portions a day vs \geq 3 portions a day) and the duration of breastfeeding (<3 months vs $>$ 3 months).

Figure 26: Reproduced from [16] - Go-NoGo activations in relation with organophosphate insecticides

In [36], a decreased fiber density in prefrontal and parietal cortices associated with higher prenatal glycol ether exposure was reported, suggesting defects in the brain circuitry underlying performance of attention, working memory and motor inhibition. These results are in line with studies reporting association between prenatal exposures to organic solvents in general and neurocognitive deficits.

Discussion

The PERINE dataset was only partially analyzed to date and further analyses of individual modalities separately or of all modalities remain to be done to assess the data more comprehensively. One hundred subjects was at the time a decent sample for MRI studies in children yet a small sample for epidemiological standards. Additional inclusion criteria were chosen to select the participants in the sub-study and keep an homogeneous sample, yet limiting variability in the data and the number of possible covariables. Besides, the low exposition dose induces more subtle effects - if any - than exposition at higher doses reported in previous studies, both in children and in adults.

Take-Home Message

- Higher maternal urinary concentrations of two of these ethers were associated with poorer child performance. High EEAA and moderate PhAA levels were associated with differential activity in frontal cortex, involved in the inhibition network ;
- Increasing levels of dimethylphosphate and diethylphosphate were associated with decreased brain activity in the left inferior and bilateral superior frontal regions during successful inhibition. We did not observe any differential activation related to inhibitory demands ;
- Decreased fiber density in prefrontal and parietal cortices associated with higher prenatal glycol ether exposure group was reported, suggesting defects in the brain circuitry underlying performance of attention, working memory and motor inhibition.
- Further analyses of individual modalities separately and of all modalities together remain to be done to assess the data more comprehensively.

Main Related Publications: [18, 16, 36, 17]

4

Conclusions and perspectives

4.1 Perspectives in MS MRI

There are short term and longer term perspectives for the projects in the field of multiple sclerosis imaging. I will present below the two main research axes for spinal cord imaging and brain imaging respectively.

Spinal cord involvement in MS: further down

EMISEP follow-up at 5 years is about to be completed. This opens an avenue for longitudinal analysis of quantitative data in MS patients. We will be able to investigate the evolution of lesions over time, as well as the evolution of normal appearing white matter through quantitative measurements. We will also investigate the correlation of these measurements with clinical data, over time and in particular at baseline to assess the predicting potential of those measurements.

In 2019, we secured additional fundings (MS-TRACTS: NCT04220814, PI: Raphaël Chouteau - CORECT CHU Rennes and myself - ARSEP) to further investigate the correlation between imaging and functional motor as well as sensitive scores measured with motor and sensitive evoked potentials in RRMS patients. The study will include sixty patients and 30 healthy controls. Another funding was obtained (MAP-MS: NCT04918225, PI: Anne Kerbrat), to explore spinal cord involvement in more advanced Primary Progressive (PPMS) patients with a particular interest for motor asymmetry. The study will include forty patients and 20 healthy controls. Both studies are bicentric studies between Rennes and Marseille and the imaging protocol was harmonized between both sites and both studies. Sagittal and axial whole spine T2-weighted conventional imaging, brain and whole spine MT imaging and brain and cervical spine MP2RAGE imaging are entailed.

The MP2RAGE sequence was proposed by Marques et al. in [100] and derives from the MPRAGE (IR-GRE) sequence. The sequence combines 2 successive contrasts with different flip angles and inversion times appropriately chosen. Since both images have exactly the same acquisition parameters apart from flip angles and inversion times, their combination can be independent of reception B1, M0 and T2* effects, providing a bias-field corrected T1 relaxometry map directly at the end of the scan. Several studies have reported the potential of the MP2RAGE sequence to detect lesions and to assess focal as well as diffuse brain damage [77, 13]. In [78], a comparison between MP2RAGE T1 values measured at 7T and post mortem analysis demonstrated the pos-

sibility to differentiate demyelinated (long T1) from remyelinated (short T1) and mixed demyelinated/remyelinated lesions (mixed T1).

In [120], the team from Marseille presented the MP2RAGE sequence for robust T1 measurement in the cervical spine with an intracenter reproducibility study. In [53], they proposed an optimized brain and cervical spine protocol yielding isotropic millimetric T1 maps in 8 minutes. In [154], Völker et al., performed a travelling head study at 7T in the context of the UK 7T network for several sequences among which MP2RAGE and reported a high reproducibility in the brain. As a ancillary study, we obtained funding from France Life Imaging to perform a travelling spine study and assess the intercenter, intersubject and intrasubject reproductibility of the brain and cervical spine MP2RAGE sequence (T1-M3C-SEP project, PI: Virginie Callot and myself).

As stated in [64], the MP2RAGE sequence appears as a robust and easy to implement sequence for clinical application in multiple sclerosis and we hope our results will contribute to confirm the potential of MP2RAGE for brain and spinal cord MS imaging, both in terms of sensitivity and of specificity to demyelination, remyelination or axonal loss.

Patient inclusions are ongoing for both MS-TRACTS and MAP-MS studies and Malo Gaubert joined the team to work on both studies and perform data analysis. Preliminary results obtained in 30 patients, show group MTR differences between RRMS and PPMS patients at the cervical level as illustrated in Figure 27 and presented at the ECTRIMS conference [57, 58].

On this sample, cervical MTR measurements were inversely correlated with EDSS scores and lesion fraction. Besides, higher lesion volume fraction were observed in the cervical spine as compared to the thoracic spine. Inclusions must be completed to further analyse the data and consolidate these results at the cervical and thoraco-lumbar levels.

Brain imaging still holds - Exploring other quantitative MRI techniques

As nicely synthetized in [64] and illustrated in Figure 28, several quantitative MRI techniques have been proposed as biomarkers for MS. Some of them can be easily be implemented on clinical scanners and their processing is also mature for clinical use. These techniques provide a way to assess remyelination, demyelination, lesion heterogeneity, lesion severity, as well as diffuse damage. Their clinical feasibility also depends on their robustness, acquisition time as well as processing time and the expertise to analyse and interpret the results.

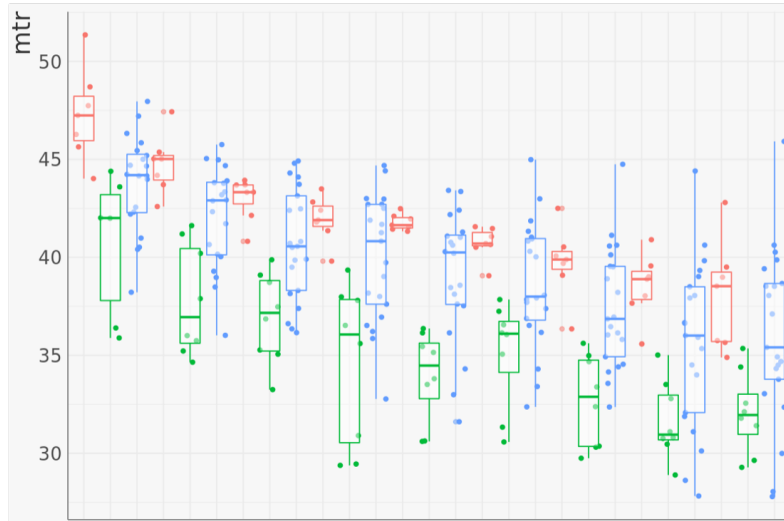


Figure 27: Preliminary results in 30 patients - MTR values per cervical level - (red) healthy controls, (blue) RRMS patients, (green) PPMS patients

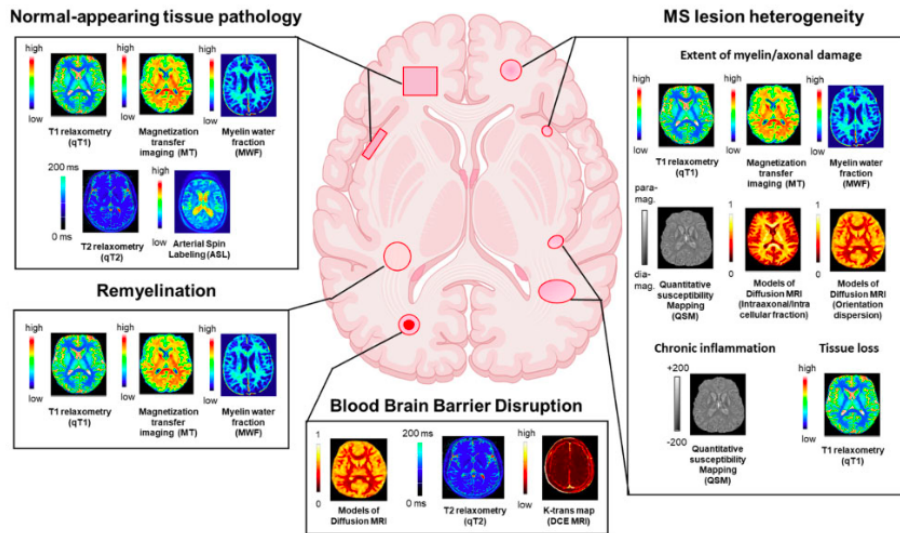


Figure 28: Reproduced from [64] - Information provided by quantitative MRI about key features of multiple sclerosis pathology for clinical applications in patients with multiple sclerosis. Quantitative MRI provides information about normal-appearing tissue pathology, multiple sclerosis lesion heterogeneity, remyelination, and blood-brain barrier disruption. dia-mag = diamagnetic; para-mag = paramagnetic

A major funding was obtained by the University Hospital of Rennes together with the University Hospital of Nantes and several other partners among which OFSEP, pharmaceutical companies and the start-up Pixyl. The project coordinated by Pr Gilles Edan and Dr Anne Kerbrat is called PRIMUS and the aim is to develop a Computer Aided Diagnosis tool for MS patients, including comparison with patients with similar clinical picture, automated segmentation of lesions and integration of new quantitative MRI metrics. The imaging workpackage I am part of involves conducting an imaging study with advanced imaging techniques that are mature enough for clinical use. This imaging study will be performed in patients from the OFSEP High Definition Cohort (OFSEP HD). We plan to include MP2RAGE, Quantitative Susceptibility Mapping (QSM), MT imaging as well as diffusion and Myelin Water Fraction (MWF) imaging.

Myelin Water Imaging has been used as a biomarker in MS clinical studies to follow demyelination and remyelination in the brain and in the cervical spine [80, 86, 87, 79]. Myelin Water Fraction maps can be obtained with different sequences among which multi spin echo (Carr Purcell Meiboom Gill - CPMG) [85] and, more recently, multi echo gradient and spin echo (GRASE) sequences [116]. The sensitivity of MWI to the presence of iron (T2*) and fiber orientation is still questioned. A variety of image processing methods has been developed over the years, some of which in our group that are still the focus of ongoing research by my colleague Olivier Commowick [30, 32, 31].

QSM is also an interesting candidate for MS quantitative clinical imaging [119, 35]. It is sensitive to diamagnetic myelin and paramagnetic iron allowing to identify active lesions without injection of contrast agent and characterise rim positive aggressive lesions [99]. Sensitivity to oxygenation state (i.e., mitochondrial functional) at 7T [50] and susceptibility network are also avenues to further explore [121] in the context of MS. Acquiring T2 gradient echo images is quite straightforward and a lot of effort has been put to develop processing methods for research purposes - the major ones are gathered in a common software interface named SEPIA [28] - as well as to bring them to the clinics through FDA approval [155].

Five french centers already involved in the OFSEP HD Cohort will take part to include 250 patients and the imaging protocol needs to be fine tuned and harmonized across centers. Data processing will be performed using tools optimised in our previous studies as well as through development and evaluation of new methods, dedicated to one modality or integrating and confronting data for several modalities. With this, we hope to provide clinicians and radiologists with biomarkers for use in clinical research studies and eventually for clinical use.

4.2 Perspectives in fMRI

I will present here three research projects involving BOLD fMRI that will be developed in the coming years. Some have started a few years ago already, data collection was recently completed or is ongoing, data processing is ongoing and publications are in preparation, the last one started more recently and is in its early stages.

Alcohol consumption in teenagers and young adults

Alcohol consumption is responsible for 3 million annual deaths worldwide (5.1% of the global burden of disease). It causes disease (liver cirrhosis, cancers, etc.) and also has social costs (injuries, road accidents, alcohol dependence, etc.). In Europe, alcohol kills 800 people every day. France has one of the highest consumption rates with 11.6 liters of pure alcohol per inhabitant in 2018. In France, alcohol is the second-ranking avoidable cause of death after tobacco with 41,000 alcohol-attributable deaths in 2015 [20] and its social cost is estimated at 120 billion euros [82]. Figures for alcohol use among young French people reveal high-risk drinking patterns: in 2017, 44% of 17 years-old declared alcohol consumption, 19.4% of those aged 18–24 got drunk regularly (at least 10 times in the last 12 months) and 13% went binge drinking at least once a week [49]. In Brittany, although the proportion of adults drinking daily is not different from other regions, all the indicators of alcohol-related accidents and deaths, as well as arrests for drunkenness, are higher than the national average. The percentage of 17-year-olds who have never drunk alcohol is 6% in Brittany compared with 14% in the whole of France according to the French Observatory for Drugs and Substance abuse (OFDT).

Excessive alcohol consumption grows through adolescence [23, 133] increases the risk of alcohol abuse [46]. This type of behavior has also been shown to have subtle but significant deleterious effects on cognitive function in adolescents [24, 59, 142, 146, 147].

Advances in the field of neuroimaging make it possible to characterize anatomical changes and the evolution of neuropsychological deficits. Indeed, excessive alcohol consumption among adolescents has been associated with MRI markers [14, 84, 96, 101, 108, 125, 135]. In particular, Pfefferbaum et al. showed a reduction in the volume and thickness of the cortex of the temporal and frontal cerebral structures in adolescents with heavy drinking compared to adolescents with light drinking [113]. Mackey et al. [96] identified that

the insula and the orbitofrontal medial cortex appear thinner in addicted individuals, regardless of the substance of interest. These links, established on the basis of anatomical and behavioral data, make it possible to identify brain structures that may induce or result in risky behavior. Robert et al. 2020 [125] showed on data from the IMAGEN cohort that gray matter development and impulsivity were associated with increased frequency of drunkenness by sex. The IMAGEN cohort is a large European consortium, which has followed more than 2000 adolescents from 14 years with acquisition at 16, 19 and now 23 years-old aiming at determining the socio-demographic, cognitive, personality, cerebral and genetics profile of reward-related disorders, including alcohol misuse, abuse and dependency. This database constitutes today the largest longitudinal population imaging database with a characterization of psychological and behavioral phenotypes (<https://imagen-europe.com/>) [134].

Not only anatomical changes but also brain function changes related to binge drinking and alcoholism can be investigated at the individual and population levels [76, 92]. In particular, the reward and inhibition circuits play a key role in the mechanisms of addiction such as alcoholism [52, 81]. Indeed, asynchronous development of these two networks may explain why adolescents have difficulty containing risky behaviours [25, 105, 141, 143].

The results obtained by Robert et al. on the IMAGEN cohort suggest that there might be both neurotoxicity-related alcohol damages on the developing brain in adolescents and structural and functional developmental changes that might put certain adolescents at-risk for greater alcohol consumption. Which developmental trajectories are the cause or consequence of alcohol intake during adolescence and are the ground bases for future alcohol dependency remains to be determined.

Besides, focusing on the societal causes of alcohol abuse, a large body of studies show that exposure to alcohol advertising through media bootstraps early consumption initiation, greater desire to drink, increased alcohol use and binge drinking patterns among young people, especially minors [54, 4, 51, 70, 130]. Although alcohol advertising content regulation has been adopted in many countries, its effects remain under-investigated. The IMAJ project is a multidisciplinary collaboration involving different research groups in Rennes: the School for Public Health (EHESP, Prof Karine Gallopel Morvan), the School of Management of Rennes (Prof Olivier Droulers, Dr Jacques-François Diouf and Prof Sophie Lacoste Badie now Professor at the University of Lille), the University of Rennes and the University Hospital of Rennes (Prof Romain Moirand and myself) and Empenn (Dr Quentin Duché and myself). The project was funded by the National Cancer Institute (PI Karine Gallopel-Morvan, NCT03818750) to investigate the effect of different

contexts and public health warnings on alcohol advertisements. Conducting this research in France has special relevance because its regulatory advertising restrictions (Evin Law) have been progressively weakened by the alcohol industry [55]. In addition, as other regions are considering implementing a similar law governing content regulation (e.g. Ireland and Scotland), it is important to conduct more research on its effectiveness.

Several measures are recommended by health actors to combat this issue: minimum unit pricing, sales ban to minor, low blood alcohol concentration for drivers, etc. A specific measure concerns alcohol advertising restriction. Some countries implemented alcohol advertising regulation laws (Poland, Sweden, Finland, Estonia, etc.), including France with the Evin law passed in 1991. This French law mandates advertising (and packaging) content to strictly convey factual information and objective qualities of alcohol products and thus bans attractive ads based on image and lifestyle evocations (seduction, power, etc.).

To our knowledge, only two studies have sought to analyze whether alcohol ad content regulation influences young people and, if so, how. Kelly, Slater and Karen showed that exposure to creative image-based alcohol ads (characters displayed in a positive context) increased alcohol appeal to young people compared to text-based ads focused on objective product qualities [72]. Chen et al. reported that television alcohol ads featuring people and animal characters, music and visual elements elicited more desire to drink and intent to purchase among young people than ads cueing objective product qualities [33]. However, these studies remain exploratory, as they detailed the persuasion process only partially, interviewed only adolescents and tested only beer brands.

In the context of the IMAJ study, self-report data as well as MRI data were collected. The imaging protocol was composed of anatomical, structural and functional sequences. A task was designed to present the participant with different ads displaying water or alcohol on a plain background or a background created by a marketing firm with a sport or party context as illustrated in Figure 29. Also, two different kinds of warning were displayed on the alcohol adds, one similar to the current french regulation (text warning), the other one with a picture and a more visible text (image warning). Two hundreds and eighty-eight different alcohol advertising contents associated or not associated to warnings were presented.

The analysis of the fMRI task aims at investigating whether, depending on the ad context (alcohol, presence of a character), warning formats displayed on ads (small and text-only vs. larger, shock-inducing and pictorial), health messages can influence brain activity by decreasing the effect of attractive

alcohol content ads on the reward system area and on behavioral responses.

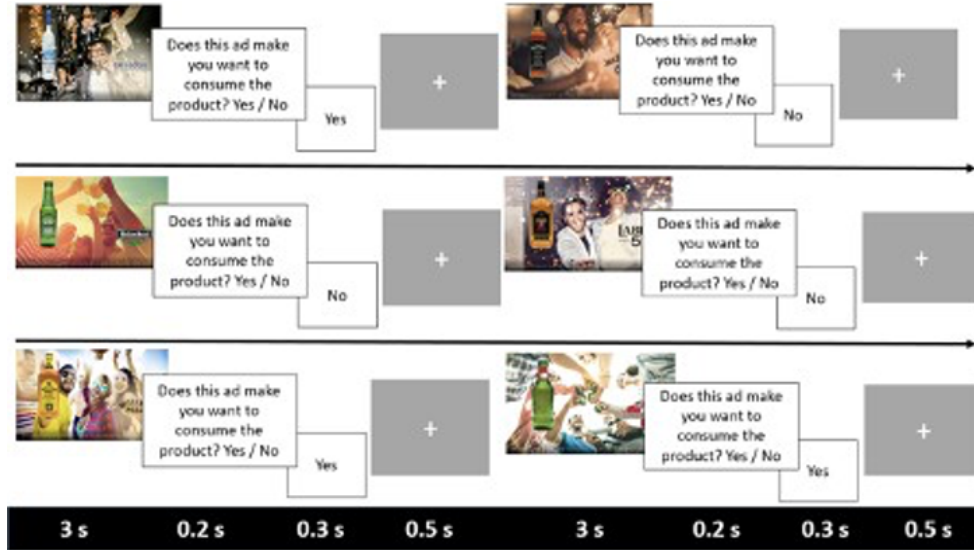


Figure 29: IMAJ task design and example ads

Preliminary analysis, focusing on the effect of ad content on the reward circuit showed significant increase activation in the fusiform gyrus, the amygdala, the medial and lateral orbito frontal cortex, caudate nucleus and hippocampus when participants were exposed to attractive ad contents for alcohol brands compared to informative ones [47]. Focusing the analysis on the effect of warnings show that image based warnings reduce activation in the reward circuit. The changes in activations in brain areas linked to emotions and the reward system plead for regulation of alcohol ad contents. Two papers are in preparation to present the results.

To build on these results and develop a collaboration with the IMAGEN consortium, I obtained an additional funding from the Institute for Clinical Research in Neuroscience (INCR). In this project named KENAVO, we aim to combine the analysis of the IMAJ and IMAGEN datasets to determine whether there are functional characteristics and external factors that can explain behavior towards alcohol and to extract biomarkers capable of predicting excessive behavior. Relying on the IMAJ dataset, we will analyze whether, depending on warning formats displayed on ads (small and text-only vs. larger, shock-inducing and pictorial), health messages can influence brain activity by decreasing the effect of attractive alcohol content ads on the reward system area and on behavioral responses. Relying on the already effective collaboration of

Dr Robert with Pr Schumann, we will explore the longitudinal anatomical and functional data from the IMAGEN cohort to extract biomarkers of alcohol consumption evolution and complement the analysis with the results obtained from the IMAJ dataset.

With regard to the IMAGEN database, the objective is to extract neurodevelopmental trajectories, in the regions of interest elicited by the IMAJ task, reward and inhibitory control networks in particular. This cohort of adolescents has been followed since the age of 14 (n=2000) with visits at 19 (n=1500) and 23 (n=1100, ongoing) and an online questionnaire at 16 (n=1700). During these visits, data on substance use (alcohol, tobacco, other drugs) is collected, which is essential to control for co-factors during the analysis of anatomical and functional brain imaging data. Functional data were acquired while participants were performing specific tasks. Among them, the stop signal task [92] allows to identify inhibitory control network while the monetary incentive task [76] activates the reward anticipation network. Functional features derived from the large database will be extracted to evaluate neurodevelopmental trajectories of these networks. Temporal dynamics of brain activation will be analyzed with mixed effects models. These analyses will be performed within a region of interest (ROI) approach. The target ROIs will be chosen from the reward system (thalamus, caudate nuclei, ventromedial prefrontal cortex, amygdala) and the inhibitory control system (parietal and prefrontal cortices). Here, we will assess how functional activity development within these ROI between 14 and 19 years, for both tasks, can predict alcohol drinking at 23 years-old. Given the potential confounding factors, we will draw particular attention to gender, tobacco and cannabis use change between 14 and 19 years and personality profile at 14 years.

On a preventive level, we hope to provide neuroimaging evidence which will influence decisions regarding alcohol marketing regulation on an important target for policymakers: males aged 18– 25. It is crucial to better understand factors that affect them as they are heavy drinkers as a group and are at risk of unprotected sex, drink-driving, suicide attempts, poor school performance and alcohol dependence in adulthood [26, 148]

On a predictive level, we expect that the developmental change of activity within the reward sensitivity and response inhibition networks between 14 and 19 years-old will be associated with alcohol intake at 23 years-old. Given the sample size of the IMAGEN cohort (around 1000 adolescents with MRI acquisition between 14 and 19 years and alcohol intake at 23 years-old), we will also explore how gender, tobacco and cannabis use change between 14 and 19 years and personality profile at 14 years might moderate these associations.

Multimodal imaging and neurofeedback

Since 2014, Neurinfo has developed expertise in the field of multimodal electroencephalography (EEG) and fMRI Neurofeedback. A software platform was set up [98] and the unimodal versus bimodal approach evaluated in [112]. Briefly, fmri and eeg compatible fmri data are collected simultaneously, processed and features are extracted in near to real time to provide the participant with a feedback. The participant is asked to explore different strategies to up or downregulate this feedback. A patient study (NCT03766113, PI: Isabelle Bonan, Simon Butet) was started in December 2018 and inclusions have just been completed with 36 patients. The dataset and the type of information that can be extracted from this dataset are presented in [91]. Pilot results are presented in [90] suggesting the potential of this approach to induce an augmented activation of ipsilesional motor areas, depending on the severity of the stroke deficit. Only the two patients with a preserved cortico-spinal tract and subcortical lesions succeeded in upregulating the ipsilesional primary motor cortex and exhibited a functional improvement of upper limb motricity. A different analysis approach was proposed in [60] using dynamic causal modelling. The results indicate that neurofeedback upregulation of targeted areas (ipsilesional supplementary and primary motor areas) not only modulated activation patterns, but also had a more widespread impact on fMRI bilateral motor networks. In particular, inter-hemispheric connectivity between premotor and primary motor regions decreased, and ipsilesional self-inhibitory connections were reduced in strength indicating an increase in activation during the NF motor task. Complete analysis will allow to consolidate these results.

Beside the context of neurofeedback, EEG-MRI can provide interesting insights in the field of dynamic functional connectivity. Due to its excellent spatial resolution, functional MRI (fMRI) has become one of the most commonly used non-invasive methods to study this connectivity. However, fMRI has a low temporal resolution which makes it very difficult to follow the dynamics of brain networks at the sub-second level. In contrast, electroencephalogram (EEG) allows the recording of brain activity with excellent temporal resolution (in the millisecond range). Complementary, diffusion imaging allows to investigate white matter trajectories and structural connectivity. Several works have shown the interest of analysing these three types of neuroimaging data in order to better characterise structural and functional connectivity, in epilepsy in particular and more generally in many neurodegenerative diseases [111, 137]. As part of a collaboration with experts in EEG, Julie Coloigner and I have started a pilot study with successive and simultaneous EEG-fMRI recordings

during rest as well as during a functional MRI task adapted from [114]. The EEG signal acquired under MRI is severely spoiled by gradient MRI artifacts and cardio-ballistic artifacts. Existing methods to remove gradient artifacts rely on the subtraction of an artifact template and cardio-ballistic artifacts remain after processing. This project is still in its preices and we are currently working on data processing to obtain quality EEG and fMRI data for further analysis.

In 2019, we acquired a Near-Infrared Spectroscopy (NIRS) system, compatible with MRI and EEG. NIRS is an optical imaging modality allowing to measure relative deoxy (Hb) and oxyhemoglobin (Hb0) concentrations [132]. NIRS provides an ecological way to assess cortical brain activity, with less time, space and cost constraints than MRI and less sensitivity to motion and interferences than EEG. There is no consensus yet on how to process the data [115] but researchers are aware of the importance of and sensitivity to processing parameters [43]. In recent years, two main softwares have emerged, namely NIRS Toolbox [128] and MNE-NIRS [93]. We have been investigating both environments and evaluated their differences on a sample dataset of 9 healthy subjects who performed simultaneous NIRS and MRI recordings during a right hand motor task performed twice. For all subjects, activation was found on the left hemisphere in agreement with BOLD fMRI which activations were systematically localized in the right-hand motor area. Five subjects show ipsilateral activations in NIRS that were not observed in BOLD. At the group level, BOLD activation was localized on the left motor cortex only when NIRS yielded bilateral activations with maximal responses on the contralateral side. Temporal correlations were variable between subjects. Although NIRS is a more recent technique and not yet ready for use at individual level, these results are encouraging.

As part of a collaboration with the Control of Eating Behaviour (EAT) group of David Val-Laillet and with Nicolas Coquery in particular, we started a project to assess fNIRS-based Neurofeedback Intervention in relation with eating behaviour and overeating (NCT05200182, PI: Nicolas Coquery, Romain Moirand). David Val-Laillet, Nicolas Coquery and myself are currently co-supervising Ambre Godet's PhD thesis, started in October 2020. As presented in her review, [61] neuroimaging and neurofeedback open new possibilities for the investigation of the neural substrates of eating behaviour and their prevention or correction. The experimental protocol involves several NIRS neurofeedback training sessions as well as simultaneous NIRS and MRI at inclusion and at one month. A pilot study was started at the beginning of 2022 and data collection was recently completed. All 15 subjects underwent all sessions successfully. Data analysis will follow to investigate the effect of neurofeedback

training as measured by NIRS and fMRI cortico-striatal connectivity as well as the correlation between NIRS cortical activations in the dorso lateral pre-frontal cortex, BOLD fMRI response in the same brain regions and in deeper regions related to the reward area. Two internships in collaboration between EAT and Empenn are scheduled next year to investigate these topics.

Clinical fMRI

For many years, we have been performing clinical fMRI examinations, generally in view of surgery, at the request of neurologists and neurosurgeons to determine language laterality and make sure primary brain areas are preserved. Language tasks (verb generation or verbal fluency) as well as motor or somaesthetic tasks are available at Neurinfo. In [19], members of the North American Society of Functional MRI (ASFNR) suggested other tasks derived from a consensus to better study language in this pre-surgical context. In [15], the six critical regions for language are described. Not only Broca and Wernicke are to be considered but also Exner's Area, the Supplementary Speech Area, the Angular Gyrus and the Basal Temporal Language Area. Several tasks need to be performed to elicit these brain regions. The authors validate those tasks against the Wada test in 22 patients and their use at the individual level. Indeed, as opposed to fMRI performed in a research context, the chosen tasks need to be very robust for use at the individual level, also in patients presenting lesions or children who may be less compliant. They must thus be wisely chosen [66]. Also, in [1], the importance of task reproducibility (across subjects) and repeatability (within subjects), measured using metrics such as Laterality Index and Center of Mass are discussed. The possible tasks are numerous and we need to evaluate them in detail in terms of activation localisation, activation ranges and robustness before proposing them to the neuroradiologist for clinical fMRI examinations. Finally, several methods exist to correct for multiple comparison that are used at the group level. These methods need to be adapted for use at the individual level, as proposed by Gorgolewski et al. [62].

Besides, no memory task is currently available for this protocol. There is a demand from epileptologists in particular, as the hippocampal region can be targeted by surgery. Banjac et al have recently proposed a memory and language task (GE2REC) [7, 6]. GE2REC consists of three inter-related tasks, sentence generation with implicit encoding (GE) and two recollection (2REC) memory tasks: recognition and recall. The task activates the fronto-temporo-

parietal language network as well as temporal mesial, prefrontal and parietal cortices. The authors have shared all the materials with us and we have started a pilot study to evaluate this task for use at Neurinfo.

Finally, with Dr. Yoann Launey, intensive care specialist, Dr. Mélanie Cogné and Dr. Simon Butet, rehabilitation specialists, we discussed the implementation of fmri for potential application in uncounscious patients and Unresponsive wakefulness syndrome (UWS) in particular. The rate of misdiagnosis in these patients remains high and BOLD fMRI can provide additional information to guide therapeutic decision. Research in this field is led by the Coma Group in Liège who initially performed a study with a tennis imagery task and a spatial navigation imagery task eliciting "wilfull", i.e., "conscious" activations in vegetative patients [110]. Liège is leading a european effort to disseminate expertise, provide recommendations, training for clinical and encouraging multimodal imaging exploration [129]. We have been associated to a grant application and hope to develop our expertise in this field thanks to this collaboration.

4.3 Conclusion

Throughout the manuscript, I have illustrated research topics I have developed since 2009. These projects started from collaborations with researchers and clinicians seeking expertise in MR imaging and fMRI at Neurinfo. Multiple Sclerosis and fMRI are the research topics I chose to invest and I have presented the research axes I intend to further develop in the coming years for both topics. One topic I did not extend on but would be keen to work on is multi-nuclei imaging, going back to my PhD work on non proton sequences and corresponding applications in particular in the field of Multiple Sclerosis. The Prisma scanner will be renewed in a few years and I hope we will have the opportunity to discuss more in details this potential evolution to sodium imaging to start with along with going for higher field strengths maybe. I hope these perspectives will allow Neurinfo to continue its development and outreach in Rennes and beyond, in the field of MR physics and clinical imaging research.

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