Imaging biomarkers in Multiple Sclerosis: from image analysis to population imaging

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Abstract

The production of imaging data in medicine increases more rapidly than the capacity of computing models to extract information from it. The grand challenges of better understanding the brain, offering better care for neurological disorders, and stimulating new drug design will not be achieved without significant advances in computational neuroscience. The road to success is to develop a new, generic, computational methodology and to confront and validate this methodology on relevant diseases with adapted computational infrastructures. This new concept sustains the need to build new research paradigms to better understand the natural history of the pathology at the early phase; to better aggregate data that will provide the most complete representation of the pathology in order to better correlate imaging with other relevant features such as clinical, biological or genetic data. In this context, one of the major challenges of neuroimaging in clinical neurosciences is to detect quantitative signs of pathological evolution as early as possible to prevent disease progression, evaluate therapeutic protocols or even better understand and model the natural history of a given neurological pathology. Many diseases encompass brain alterations often not visible on conventional MRI sequences, especially in normal appearing brain tissues (NABT). MRI has often a low specificity for differentiating between possible pathological changes which could help in discriminating between the different pathological stages or grades. The objective of medical image analysis procedures is to define new quantitative neuroimaging biomarkers to track the evolution of the pathology at different levels. This paper illustrates this issue in one acute neuro-inflammatory pathology: Multiple Sclerosis (MS). It exhibits the current medical image analysis approaches and explains how this field of research will evolve in the next decade to integrate larger scale of information at the temporal, cellular, structural and morphological levels.

1. Introduction

In medicine, the pace of change in data production is far outstripping the capacity of existing computing models. This increase of data stimulates the need to guide the clinicians within the mass of information to integrate into the medical decision process. This is acutely challenging for brain diseases where the main challenges facing us today include 1) increasing our understanding of central nervous system (CNS), 2) undertaking more effective monitoring of therapeutic procedures, 3) modeling groups of normal and pathological individuals (cohorts) through image descriptors and 4) stimulating new drug design. To address these challenges, current practice is missing computational models able to correlate the large amount of observations produced on patients to underlying pathological phenomena, frameworks to validate these models, and infrastructures to learn these models and apply them to large populations of patients. These issues pose new challenges in the field of medical image analysis, in terms of developing new integrated computational models of living organs and systems capable of mining image descriptors from big databases, assimilating the quantity of imaging data produced about a given patient through compact and relevant mathematical representations, learning dynamics of spatiotemporal data to predict the disease course in individual patients, and reconciling observation and treatment processes (the *theragnostics* concept). Once these major advances will be achieved, the face of clinical practice will change both for professionals (innovations in clinical services, treatment delivery, training and education) and for citizens (safer, faster and more accurate medicine).

In this paper, we propose to illustrate the relevance of this evolution of the medical image analysis domain in one acute neuro-inflammatory pathology: multiple sclerosis (MS). We show how computational models have been used in the past to provide some relevant, though limited, markers of the disease and its evolution, but also why these existing computational solutions are limited and how they will evolve in the next decade in order to tackle the remaining challenges and provide imaging biomarkers that become capable of discovering quantitative image descriptors that are not necessarily visible to the human eye and use these descriptors to better represent the dynamics of the pathology and accurately predict the disease course in individual patients.

2. Context: Imaging Biomarkers in Multiple Sclerosis

MS is a chronic autoimmune demyelinating disorder of the CNS. It is the principal cause of severe, non-traumatic disability among young adults, affecting more than half a million people in Europe. It has a prevalence rate of 83 per 100,000, and a female:male ratio of nearly 3:1. Onset usually occurs before the age of 30, that is, at a crucial point in an individual's personal, family, professional and social lives. It leads to permanent disability for decades, but has only a marginal effect on life expectancy. MS induces a huge, rapidly increasing, financial burden on society, owing to the approval and more widespread use of new disease-modifying treatments. Disability accumulation in MS is generally acknowledged to be correlated with axonal injury, itself being correlated with the degree of inflammation. However, the interdependence between inflammation and neuro-degeneration, and their respective contributions to clinical deficits remain unclear. Recent epidemiological data from our group suggest that MS is a two-stage neurodegenerative inflammatory disease (see (Leray et al., 2010). At each stage, the disease progression follows a different physiopathological pathway: highly variable in the first stage (EDSS < 3), but broadly similar for the whole population in the second stage (EDSS > 3). This new concept highlights the need for a better definition of the early stage, starting with the very first event (clinically isolated syndrome, CIS), and for new research paradigms to better characterize and monitor the progression of the pathology in individual patients.

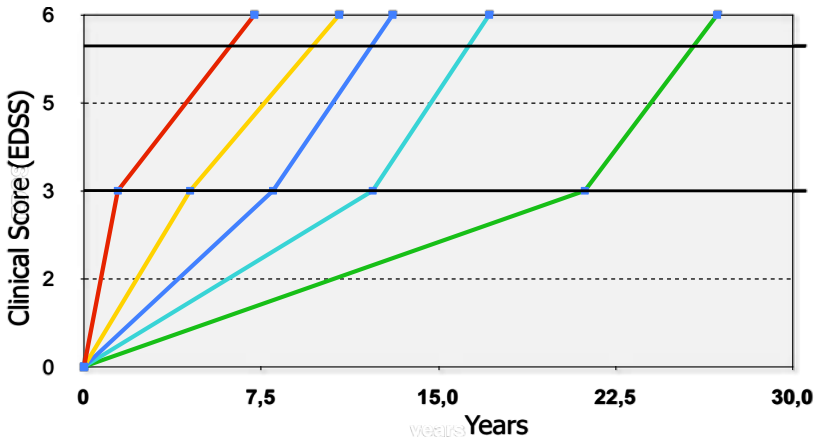

Figure 1: Epidemiologic study of natural evolution of Multiple Sclerosis disease as a 2-stage course. At onset (time=0), a new CIS patient may take from 2 (red) to more than 20 (green) years to reach a clinical score highlighting acute handicap (EDSS=3). Why there is such discrepancy in the population, or why a patient will evolve in the "red" group or in the "green" one is mostly unknown. Having therapy to move a patient from one group (e.g. red) to another (e.g. green) cannot be set up without objective figures to validate this new drug. Imaging is today the only expected instrument to respond to these questions since it is mostly non invasive and can potentially be specific and sensitive (*Study from 2054 MS patients, Univ. Hospital Rennes*).

In recent years, conventional magnetic resonance imaging (MRI) has emerged as a powerful noninvasive tool for diagnosis, description of the natural history of the disease and treatment monitoring of MS. In addition, MRI findings have been used to explore drug efficacy in clinical trials.

A number of MR studies show that the principal pathological substrate of permanent disability is axonal loss, detected in MR studies as global atrophy but also as regional atrophy in the white (WM) or grey matter (GM). This atrophy already occurs at early stages of the disease. Axons contribute to about 50% of the WM volume and are, together with neurons, the main contributors of the GM volume. In early progressive MS, GM atrophy seems to be more prominent than WM loss (Dalton et al., 2004; Simon et al., 1999). Longitudinal MR studies in CIS patients have demonstrated that early rather than later focal lesion accumulation is predictive of conversion from CIS to definite MS, accumulation of clinical deficit (Brex et al., 2002; O'Riordan et al., 1998), but also of subsequent brain atrophy. Today, it is not possible to determine exactly when atrophy begins even though it is detectable in CIS cohorts and in early MS patients. Such a knowledge would be important not only for prognostic issues per se, but also crucial to select patients at risk for a severe disease course and to start treatment with disease modifying drugs as early as possible. The need for robust predictive imaging disease markers in MS at presentation is demonstrated by the findings of Brex and colleagues (Brex et al., 2002): after a mean follow-up of about 14 years of CIS patients, about 12% with four or more focal T2-weighted MR lesions did not develop clinically definite MS (CDMS), and thereof only about 40% were only mildly disabled. In the CIS group with one to three focal MR lesions at presentation about one third develops moderate to severe disability after 14 years follow-up. About 90% of CIS patients with one to three MR lesions at presentation develop CDMS 14 years later. Furthermore, using conventional MR methodology in clinical trials of CIS patients, a high proportion of treated patients continue to have MRI activity. MRI measures of inflammation in Relapsing Remitting MS (RRMS) or Secondary Progressive MS (SPMS), such as Gd-enhancement, do not correlate with clinical disability at 1 to 2 years follow-up (Kappos et al., 1999). In conventional MRI studies, Gadolinium enhancement (Gd-DTPA) reflects a severe focal breakdown of the blood-brain barrier (BBB) but this breakdown does not really predict the severity of the pathology evolution.

These different studies show that conventional MRI surrogates provide information at the macroscopic level but lack sensitivity and specificity in identifying the full extent of underlying MS pathology. They also show relatively weak relationships to clinical status such as predictive strength for clinical change (called the *clinical-MRI paradox*) (Barkhof, 2002). With the advent of disease modifying drugs, there is a need for robust and specific MR markers to characterize the pathology especially at onset where patients have high risk to develop MS or a more severe disease course.

The "*clinical-MRI paradox*" is defined as the absence of correlation between clinical disability, and the predictive value of MRI in MS. This paradox prohibits the use of imaging as a primary outcome parameter in certification of new drugs. It is assumed that this paradox could be partly due to the lack of MRI specificity related to the heterogeneous pathological substrates of MS and to its inability to quantify the extent of damage in the normal-appearing brain tissues (NABT), i.e. the invisible pathology. It is then expected that non-conventional MRI techniques, such as Magnetization Transfer MRI (MTI), Relaxometry, Diffusion Tensor Imaging (DTI), Chemical Shift Imaging (CSI), will be able to alleviate these limitations by providing information about structural and biochemical changes occurring within and outside MS lesions, in particular in the NABT. These techniques could also significantly improve the monitoring of the inflammatory demyelination and the axonal loss (Bakshi et al., 2008).

Current medical image analysis methods addressing this issue have still a very limited scope, especially in their ability to assimilate a large amount and large variety of information. Current data processing technologies focus mostly on pre-processing of conventional MRI, especially on data fusion (registration between modalities, patients and atlases), on multimodal cross sectional image segmentation or longitudinal MRI intensity evolution of macroscopic lesions (usually up to 3 MRI sequences), on estimation of regional and global deformations to exhibit atrophy, and on coarse differential detection of diffuse pathology from diffusion MRI (mostly performed on scalar maps). Current data processing strategies still remain limited to overcome all the limitations of MRI in MS. As such, the methods still work on a very limited variety of images able to measure the real early process, and rather address later or non-specific pathological stages. The current image processing methods assimilate a large but still limited amount of information; they are barely addressing the issue of compact feature selection and representation; or barely addressing the issue of learning

spatio-temporal disease pattern models. Finally, they are not addressing the issue of generalization of disease model to derive individual tests and provide prospective figures for individual patient follow-up (Crimi et al., 2014).

To summarize, the advent of disease-modifying drugs has created the need for robust and specific imaging markers to characterize the pathology of MS patients and thus identify those with a high risk of developing a more severe disease course at onset.

3. Image processing in Multiple Sclerosis

3.1. Context

Today, measures from MRI complement and enrich the clinical observations based on scales such as the expanded disability status scale (EDSS) or the MS functional composite (MSFC) whose drawbacks are numerous. Clinical observations are inherently subjective, show poor inter- and intra-observer reliability, have limited sensitivity to change compared with MRI (up to 15 times more sensitive in longitudinal studies). MRI is currently used for assessing the disease burden and progression by counting the number of T2w MRI lesions, and the number of lesions on gadolinium-enhanced T1w MRI. In this context, a large set of medical image processing methods have been developed in recent years to address these issues.

3.2. Image processing in MS

Current computer assisted analysis of MR images in MS requires the application of complex image processing workflows. These workflows usually encompass standard pre-processing stages such as noise removal, non-uniformity intensity correction, intensity normalization, spatial normalization, skull-stripping which removes non brain tissues from the image and focal WM and GM lesion segmentation. Among this workflow, *noise reduction* is necessary as image intensities are corrupted by additive noise that must be limited to improve the signal-to-noise ratio. In general, image noise comes from MR hardware (RF coil, or pre-amplifier, and MR sequence optimization). Numerous methods for image denoising have been proposed in general image processing, reviewed in (Buades et al., 2005). A new denoising algorithm, non-local means (NLM), has been proposed by (Coupe et al., 2008) for different medical image acquisition techniques and more specifically for MRI, demonstrating a clear impact in processing MRI in MS. Another image artefact correction concerns the *intensity inhomogeneity correction*. Vovk et al and Hou (Hou, 2006; Vovk et

al., 2007) recently reviewed various inhomogeneity correction methods. In principle, these artefacts are due to image instrumentation and related to artefacts caused by slow, non-anatomic intensity variations of the same tissue over an image domain. If left uncorrected, such an artefact precludes direct comparison of voxel intensities. *Spatial normalization* concerns the issue of gathering into the same geometric referential system all images that are used by the processing workflow. Numerous methods have been proposed in this very active field of research (Maintz and Viergever, 1998). *Intensity normalization* is another processing needed that is particularly acute when the frequency of the acquisitions is in the range of months or years (Karpate et al., 2014). Finally, *skull stripping/brain extraction* is usually performed in order to ease MS lesions segmentation, in order to remove non-brain tissues from the images, see for instance (Fennema-Notestine et al., 2006; Iglesias et al., 2011) for a large review and comparison of these methods.

The last stage of the image processing workflows concerns the detection and segmentation of MS lesions (MSL) from brain magnetic resonance images (MRI). Automatic MSL detection and recognition is a topic of still growing importance and still challenging. Although manual lesion detection by experts is still considered as a Gold Standard, which is quite questionable because of the very large discrepancy existing between experts, the objective evaluation of lesions becomes difficult for the radiologist when the number and the resolution of MRI sequences get larger.

Macroscopic MS lesions segmentation is performed on multimodal cross-sectional images. These segmentation methods can be classified according to the level of interaction needed for lesion delineation and the nature and number of MRI sequences used (usually up to 3), see (Lladó et al., 2012) for a recent review. A further distinction can be made between data-driven methods and supervised learning methods. One breed of unsupervised MSL segmentation includes Gaussian Mixture Modeling (GMM) on multispectral MRI, where each multivariate Gaussian probability density function represents a normal appearing brain tissue (Van Leemput et al., 2001). The GMM enables characterization of the image intensities with a reduced number of parameters, which are estimated by a maximum likelihood estimator (MLE). An effective approach in this domain is to consider MS lesions as outliers from NABT (Garcia-Lorenzo et al., 2011; Van Leemput et al., 2001). Supervised methods (often related to Machine Learning) require images that have already been segmented in order to "learn" how to segment the lesions. Examples in this field are spatial

decision forests (Geremia et al., 2011), one-class SVM (Karpate et al., 2015a), sparse dictionary learning (Deshpande et al., 2015) or deep learning (Brosch et al., 2016). Frameworks for segmentation of gadolinium-enhancing lesions were also developed for instance through robust statistics on image intensities (Karpate et al., 2015b) or probabilistic methods using conditional random fields (Karimaghaloo et al., 2012).

Integration of these MS lesion patterns into a computational decision making process is still rare. Recent advances have been proposed to correlate the inflammatory patterns of MS lesions with the risk of evolution of the pathology by using enhanced patterns coming from both Gadolinium and a new contrast agent (USPIO) marking early attacks of macrophages responsible to the advent of lesions (see Figure 3). Thanks to these approaches, it has been demonstrated that patients at onset having specific early patterns of inflammatory lesions were correlated with a higher lesion load later in the disease progression, therefore having a higher risk of developing a severe course of the disease (Crimi et al., 2014).

3.3. Image processing of non-conventional MRI

Quantitative imaging in MS (qMRI) techniques, including diffusion tensor imaging (DTI), magnetization transfer imaging (MTI), relaxometry and MR spectroscopy, though not used yet in the clinics, have been found to provide useful information about the extent of the diffuse tissue injuries (outside lesions) observed in MS patients in both stages of the disease, thereby contributing to our understanding of its pathophysiology (Bakshi et al., 2008; Miller, 2004). For example, DTI studies illustrate an increase in mean diffusivity (MD) and a decrease in fractional anisotropy (FA), while MTI shows a decrease in MT ratio in MS patients related to both demyelination and axonal loss, particularly in lesion regions but also in normal-appearing WM (NAWM) and GM. These studies often require control participants with whom patients can be compared. For DTI, scalar measures may lose some of the information contained in the diffusion tensors, but it has been shown recently that using the whole tensor can improve the detection power in MS. Registration of new diffusion models

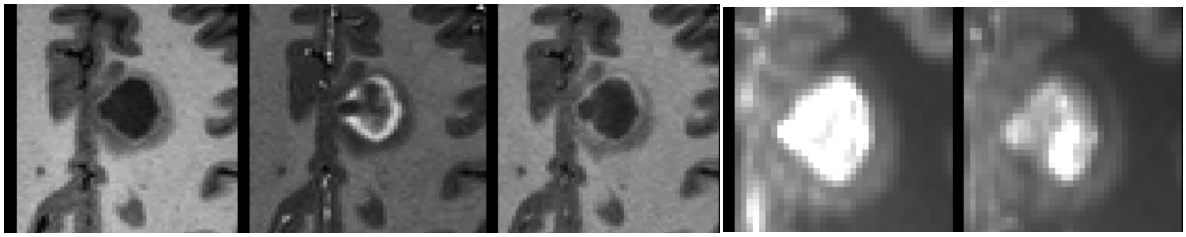

Figure 2: Sample image signature of a lesion from the protocol, images (and day) from left to right: T1-w (D1), T1-Gd (D1), T1-w USPIO (D2), T1 relaxometry (D1), T1 relaxometry with USPIO (D2)**.**

(including multiple compartments) was also devised for the robust detection of patient to population differences with small databases using non local approaches. This work allowed obtaining meaningful detections of differences in multiple sclerosis, with a similar precision as with large control databases (Commowick et al., 2008; Commowick et al., 2015). In addition, merging all these complementary parameters derived from different modalities (e.g., DTI, MTI ratio maps and relaxometry) is still very challenging, owing to the variations in their spatial resolution and artefact sensitivity (Soustelle et al., 2015). There is still a need for significant research efforts to integrate the microstructural quantitative MR information in a common template.

Metabolic and hemodynamic characterization of compartments in MS: Whereas spectroscopic proton imaging (or chemical shift imaging - CSI) has become a useful clinical tool for characterizing metabolic disorders or grading tumors, processing CSI data along with complementary qMRI data is still a challenge in MS, as none of the processing packages that are currently available provide the entire set of modules required for such a project. Similarly, while some preliminary studies have shown that local WM and GM perfusion defects can be a precursor of pathology progression in MS, none of the current data analysis frameworks are capable of integrating and processing such functional and metabolic recordings with qMRI, let alone with cell-specific imaging.

4. Perspectives : How to go beyond the clinical-MRI paradox?

Current medical image analysis methods are mostly directed towards the detection of what is visible to the human eye. New image processing mechanisms need to be introduced in order to quantify the pathology even if the defects are not directly visible. Data-processing strategies remain too limited to overcome the medical imaging challenge in MS. Existing methods work on a very limited number of observations and patients, they assimilate a large, but still limited amount of information. They fail at addressing the issues of compact feature selection and representation, learning spatiotemporal disease pattern models, and generalization of disease models to derive individual tests and provide prospective figures for the follow-up of individual patients. This evolution requires the advent of new imaging protocols available in clinics and able to provide quantitative information (whereas conventional MRI usually provides only qualitative values), new computational models and data processing methods able to handle these high dimensional data, and the advent of

computational infrastructures that will process large datasets in order to foster the statistical power of the computational models.

To match these objectives, we will need to create new clinical-compliant methods for quantification of the diffuse inflammation, demyelination and axonal loss particularly from molecular/cellular specific imaging and non-conventional MRI. As illustrated on Figure 3, this will require to delineate neural circuits and to characterize tissue microstructure present in these circuits. There is therefore a need for novel imaging techniques (acquisition and processing) to non-invasively characterize alterations in tissue compartments associated with disease progression. In addition, the spatial location of lesions with respect to these neural circuits likely plays a central role in the progression of disease burden. To address this paradox between clinical and MRI observations, new computational solutions will be developed in order to better characterize the tissue microstructure from diffusion MRI. We need to implement new mathematical models of diffusion imaging able to perform direct modelling of the displacement of water molecules under directional diffusion under limited scanning time (Stamm et al., 2012) (Hédouin et al., 2015), and able to quantify the diffuse, invisible defects of the brain tissues. Similarly, we need to incorporate new relaxometry imaging techniques and reconstruction techniques to identify brain tissue compartments. As recently stated by the concept of fingerprinting (Ma et al., 2013), normal brain tissue consists of tissue compartments that exhibit ranges of T1 and T2 contrast, including myelin-bound water, extra-axonal water, and cerebrospinal fluid. There is a pressing need to move from voxel level to tissue compartment level measures of disease burden and MS lesion severity. Current imaging techniques take too long to identify these compartments for clinical usage, and provide poor spatial resolution. However, direct measurement of myelin-bound water,

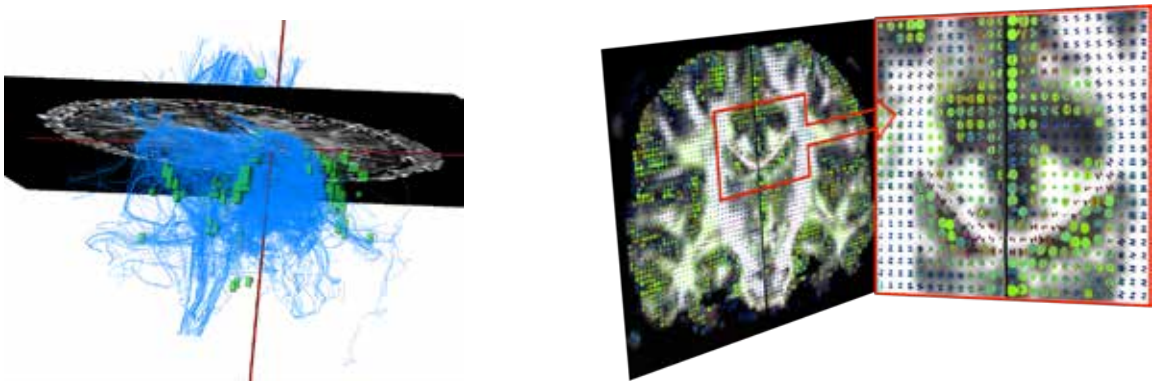

Figure 3: Illustration of the diffuse model concept, (left) regular tractography going though MS lesions, (right) new diffusion model providing high order diffusion MRI parameters from low angular resolution acquisitions

and other tissue diffusion compartments, will provide critical new insight into lesion burden (Stikov et al., 2015).

Another shift in imaging the MS pathology concerns a better characterization of the inflammatory process as it occurs at the early stage. Neuropathological in vitro studies suggest that, in active MS lesions at an early or chronic stage (i.e. the "first stage"), the acute axonal injury detected by amyloid precursor protein (APP) correlates quantitatively with the number of inflammatory cells, especially macrophages (Bitsch et al., 2000), and axonal injury is a major substrate for permanent neurological disability in MS patients. This knowledge would be important not only for prognostic issues per se, but also – crucially – for identifying patients at risk of following a more severe disease course, in order to start treating them with more aggressive disease-modifying drugs as early as possible. Imaging the neuro-inflammation through cell labeling neuroimaging then becomes crucial for the definition of new imaging biomarkers able to exhibit specific signatures such as inflammatory cells visible with USPIO, Gd contrast agents on MRI, or with PET signatures from dedicated fluorine-18-labeled second-generation TSPO ligands.

However, one requirement for a large dissemination of these new imaging technologies to researchers or clinicians in the clinical neuroscience domain is to set up large-scale studies or longitudinal follow-ups involving large samples and several image modalities, time points, and acquisition centers. This ambition requires the advent of computational infrastructures and shared and advanced image processing methodologies to more efficiently compute quantitative parameters from multiple, spatiotemporal imaging sequences. This ambition is still a challenge due to the lack of resources and capabilities to locally recruit subjects who meet specific inclusion criteria. This motivates the need for sharing the load over computational infrastructures in order to produce, store and process the relevant imaging data. For these reasons, enabling the pooling of experimental results and processing workflows between collaborative centers will allow to recruit large and more specific populations of patients; to model and mine new image descriptors from large databases; to assimilate a large quantity of imaging data produced on a specific population, and finally to amplify scientific results by efficient exploration of multiple computational models tested on these distributed experimental study data.

5. References

Bakshi, R., Thompson, A.J., Rocca, M.A., Pelletier, D., Dousset, V., Barkhof, F., . . . Filippi, M., 2008. MRI in multiple sclerosis: current status and future prospects. Lancet Neurol 7, 615-625.

Barkhof, F., 2002. The clinico-radiological paradox in multiple sclerosis revisited. Curr Opin Neurol 15, 239-245.

Bitsch, A., Schuchardt, J., Bunkowski, S., Kuhlmann, T., Brück, W., 2000. Acute axonal injury in multiple sclerosis. Correlation with demyelination and inflammation. Brain: A Journal of Neurology 123 (Pt 6), 1174-1183.

Brex, P.A., Ciccarelli, O., O'Riordan, J.I., Sailer, M., Thompson, A.J., Miller, D.H., 2002. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. The New England Journal of Medicine 346, 158-164.

Brosch, T., Tang, L., Yoo, Y., Li, D., Traboulsee, A., Tam, R., 2016. Deep 3D Convolutional Encoder Networks with Shortcuts for Multiscale Feature Integration Applied to Multiple Sclerosis Lesion Segmentation. IEEE Transactions on Medical Imaging.

Buades, A., Coll, B., Morel, J.M., 2005. A review of image denoising algorithms, with a new one. . Multiscale Modeling & Simulation 4, 490-530.

Commowick, O., Fillard, P., Clatz, O., Warfield, S.K., 2008. Detection of DTI White Matter Abnormalities in Multiple Sclerosis Patients. Proceedings of the 11th International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI'08), Part I, pp. 975-982.

Commowick, O., Maarouf, A., Ferré, J.-C., Ranjeva, J.-P., Edan, G., Barillot, C., 2015. Diffusion MRI abnormalities detection with orientation distribution functions: A multiple sclerosis longitudinal study. Medical Image Analysis 22, 114-123.

Coupe, P., Yger, P., Prima, S., Hellier, P., Kervrann, C., Barillot, C., 2008. An optimized blockwise nonlocal means denoising filter for 3-D magnetic resonance images. IEEE Transactions on Medical Imaging 27, 425-441.

Crimi, A., Commowick, O., Maarouf, A., Ferre, J.C., Bannier, E., Tourbah, A., . . . Barillot, C., 2014. Predictive Value of Imaging Markers at Multiple Sclerosis Disease Onset Based on Gadolinium- and USPIO-Enhanced MRI and Machine Learning. PLOS-ONE 9, e93024.

Dalton, C.M., Chard, D.T., Davies, G.R., Miszkiel, K.A., Altmann, D.R., Fernando, K., . . . Miller, D.H., 2004. Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. Brain: A Journal of Neurology 127, 1101-1107.

Deshpande, H., Maurel, P., Barillot, C., 2015. Classification of Multiple Sclerosis Lesions using Adaptive Dictionary Learning. Computerized Medical Imaging and Graphics 46, 2-10.

Fennema-Notestine, C., Ozyurt, I.B., Clark, C.P., Morris, S., Bischoff-Grethe, A., Bondi, M.W., . . . Brown, G.G., 2006. Quantitative evaluation of automated skull-stripping methods applied to contemporary and legacy images: effects of diagnosis, bias correction, and slice location. Hum Brain Mapp 27, 99-113.

Garcia-Lorenzo, D., Prima, S., Arnold, D.L., Collins, D.L., Barillot, C., 2011. Trimmed-Likelihood Estimation for Focal Lesions and Tissue Segmentation in Multi-Sequence MRI for Multiple Sclerosis. IEEE Transactions on Medical Imaging 30, 1455-1467.

Geremia, E., Clatz, O., Menze, B.H., Konukoglu, E., Criminisi, A., Ayache, N., 2011. Spatial decision forests for MS lesion segmentation in multi-channel magnetic resonance images. NeuroImage 57, 378-390.

Hédouin, R., Commowick, O., Stamm, A., Barillot, C., 2015. Interpolation and Averaging of Multi-Compartment Model Images. In: Navab, N., Hornegger, J., Wells, W., Frangi, A. (Eds.), Medical Image Computing and Computer-Assisted Intervention -- MICCAI 2015. Springer, pp. 354-362.

Hou, Z., 2006. A review on MR image intensity inhomogeneity correction. International Journal of Biomedical Imaging 2006, 1-11.

Iglesias, J.E., Liu, C.Y., Thompson, P.M., Tu, Z., 2011. Robust brain extraction across datasets and comparison with publicly available methods. IEEE Transactions on Medical Imaging 30, 1617-1634.

Kappos, L., Moeri, D., Radue, E.W., Schoetzau, A., Schweikert, K., Barkhof, F., . . . Filippi, M., 1999. Predictive value of gadolinium-enhanced magnetic resonance imaging for relapse rate and changes in disability or impairment in multiple sclerosis: a meta-analysis. Gadolinium MRI Meta-analysis Group. Lancet 353, 964-969.

Karimaghaloo, Z., Shah, M., Francis, S.J., Arnold, D.L., Collins, D.L., Arbel, T., 2012. Automatic detection of gadolinium-enhancing multiple sclerosis lesions in brain MRI using conditional random fields. IEEE Transactions on Medical Imaging 31, 1181-1194.

Karpate, Y., Commowick, O., Barillot, C., 2015a. Probabilistic One Class Learning for Automatic Detection of Multiple Sclerosis Lesions. IEEE International Symposium on Biomedical Imaging (ISBI), Brooklyn, United States.

Karpate, Y., Commowick, O., Barillot, C., 2015b. Robust Detection of Multiple Sclerosis Lesions from Intensity-Normalized Multi-Channel MRI. SPIE Medical Imaging, Orlando, United States.

Karpate, Y., Commowick, O., Edan, G., Barillot, C., 2014. Longitudinal Intensity Normalization in Multiple Sclerosis Patients. Miccai Workshop on Clinical Image-Based Procedures. Translational Research in Medical Imaging. Springer-Verlag, Boston, MA, pp. 1-8.

Leray, E., Yaouanq, J., Le Page, E., Coustans, M., Laplaud, D., Oger, J., Edan, G., 2010. Evidence for a two-stage disability progression in multiple sclerosis. Brain 133, 1900-1913.

Lladó, X., Oliver, A., Cabezas, M., Freixenet, J., Vilanova, J.C., Quiles, A., . . . Rovira, À., 2012. Segmentation of multiple sclerosis lesions in brain MRI: A review of automated approaches. Information Sciences 186, 164-185.

Ma, D., Gulani, V., Seiberlich, N., Liu, K., Sunshine, J.L., Duerk, J.L., Griswold, M.A., 2013. Magnetic resonance fingerprinting. Nature 495, 187-192.

Maintz, J., Viergever, M., 1998. A survey of medical image registration. Medical Image Analysis 2, 1-36.

Miller, D.H., 2004. Biomarkers and Surrogate Outcomes in Neurodegenerative Disease: Lessons from Multiple Sclerosis. NeuroRx 1, 284-294.

O'Riordan, J.I., Thompson, A.J., Kingsley, D.P., MacManus, D.G., Kendall, B.E., Rudge, P., . . . Miller, D.H., 1998. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain: A Journal of Neurology 121 (Pt 3), 495-503.

Simon, J.H., Jacobs, L.D., Campion, M.K., Rudick, R.A., Cookfair, D.L., Herndon, R.M., . . . Brownscheidle, C.M., 1999. A longitudinal study of brain atrophy in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Neurology 53, 139-148.

Soustelle, L., Commowick, O., Bannier, E., Barillot, C., 2015. Quantification of Myelin Degeneration in Multiple Sclerosis within Clinical Scan Times. ISMRM, Toronto, Canada.

Stamm, A., Perez, P., Barillot, C., 2012. A new multi-fiber model for low angular resolution diffusion MRI. Biomedical Imaging (ISBI), 2012 9th IEEE International Symposium on, pp. 936-939.

Stikov, N., Campbell, J.S., Stroh, T., Lavelee, M., Frey, S., Novek, J., . . . Pike, G.B., 2015. In vivo histology of the myelin g-ratio with magnetic resonance imaging. NeuroImage 118, 397-405.

Van Leemput, K., Maes, F., Vandermeulen, D., Colchester, A., Suetens, P., 2001. Automated segmentation of multiple sclerosis lesions by model outlier detection. IEEE Transactions on Medical Imaging 20, 677-688.

Vovk, U., Pernus, F., Likar, B., 2007. A review of methods for correction of intensity inhomogeneity in MRI. IEEE Transactions on Medical Imaging 26, 405-421.