Translation of Computer-Assisted MRI Assessments of Multiple Sclerosis to Clinical Care

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MSPie served as a prototype platform to optimize and validate the performance of parts of the AI-Rad Companion Brain MR product solution.

Key points

- Standardized volumetric MRI follow-up protocols
- Fully automatic MRI data routing
- Immediate volumetric MRI analysis
- Computer-assisted monitoring
- Interactive results editing and report generation

Background

The Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS; https://www.mspaths.com) is a Biogen-sponsored network that aims to standardize and quantify clinical, radiological, and biomarker assessments of MS in routine clinical practice, with the ultimate goals of enabling personalized medicine and large-scale real-world research. For the imaging assessments, the intention is to provide highly precise, automated quantification of disease-specific volumetric changes of both MS lesions and normalized brain volume. Mainly sub-clinical in nature, these MRI changes over time can provide important information on disease severity and response to disease modifying therapies [1].

In 2009, the concept of an MS treatment target termed, "no evidence of disease activity" (NEDA) arose from a retrospective analysis of clinical trial data [2], with the original definition consisting of no relapses, no disability progression, and no MRI-based disease activity markers, i.e., no gadolinium enhancing lesions or new or enlarging T2 lesions. Subsequently, further development of the NEDA definition led to the incor-

Parameter	3D FLAIR MS-P	3D T1 MS-P
Brain coverage	Full	Full
Acquired pre-contrast	Pre-contrast	Pre-contrast
Orientation	Sagittal	Sagittal
MR acquisition type	3D	3D
Repetition time (ms)	5000	2300
Echo time (ms)	392–394	2.96–2.98
Inversion time (ms)	1800	900
Flip angle (deg)	120	9
Read FOV (mm)	256	256
Phase FOV (mm)	240	240
Percent FOV (%)	93.8	93.8
No. phase encoding steps	221	239
Phase encoding direction	A >> P	A >> P
Slice thickness (mm)	1	1
Pixel spacing (mm)	1 × 1	1 × 1
Pixel bandwidth (Hz/Px)	780	240

Table 1: The standardized MS PATHS acquisition protocol. This MRI protocol was implemented on available 3T scanners from Siemens Healthineers within all participating MS PATHS centers allowing optimal regional monitoring and inter-institutional comparison.

poration of the annualized rate of brain volume loss [3]. Based on recent imaging protocol and monitoring recommendations [4, 5], standardized imaging data acquisition forms the basis towards individual precision medicine monitoring in MS when supplemented by computer-aided evaluation technology.

The concept of new or enlarging T2 lesions (NET2L) as a marker of MS inflammatory activity is based on the understanding that the vast majority of gadolinium-enhancing lesions evolve into permanent T2 lesions. In addition, the growth of chronic inflammatory active lesions is yet another recognized marker of disease activity. The occurrence of NET2L in MS under treatment is considered evidence of therapy insufficiency or even failure [3].

The gradual loss of brain volume over lifetime represents a physiological process termed atrophy. Brain atrophy however intensifies and accelerates in MS, constituting the accumulative result of tissue destruction [6]. Therefore, (1) the cross-sectional comparison of individual brain volume measures with age-matched control groups and (2) the determination of the brain atrophy rate over defined intervals are measurable determinants of non-physiological brain atrophy. To normalize overall brain volume measures, brain tissue volume is typically normalized using the individually stable intracranial volume. The resulting ratio is called brain parenchymal fraction (BPF) and thus allows inter-individual comparison [7]. Although disease-modifying therapies attenuate brain volume loss in MS [8], the use of brain atrophy as a clinical marker of disease progression in individual patients is still subject of debate [9].

To realize the goals of reliable, quantitative MRI metrics in the MS PATHS network, Biogen initiated a collaboration with Siemens Healthineers to jointly develop the MS PATHS image evaluation (MSPie) software.[1] This *syngo*.via Frontier-based prototype enabled optimization and validation of the employed algorithms within the clinical workflow in a close collaboration between the University Hospital Dresden, other MS PATHS partners, Biogen and Siemens Healthineers. To this end, the prototype has an interactive user interface and means to correct the results. The final product which is available within the AI-Rad Companion Brain MR suite incorporates the learnings which were gained from MSPie and is a fully automatic, non-interactive solution. Here, we present the results of our initial experience with translating this development to the point of care.

[1] *Work in progress. The application is currently under development and is not for sale in the U.S. and in other countries. Its future availability cannot be ensured.*

1 The graphical user interface provides a full screen presentation of segmentation and comparison results combined with a collection of numerical and graphical evaluations and a separate articulated control area for interactive lesion editing. Reformats can be adapted to coronal or sagittal viewing habits.

Methods

Standardized follow-up brain MRI acquisition

The use of MRI to measure MS disease activity and progression required minimal adjustments in primary data acquisition to ensure high sensitivity to changes over time [10]. The MS PATHS network therefore agreed to harmonize their institutional scanner protocols across all 3T MRI scanners from Siemens Healthineers at participating centers.

Core sequences are a 3D fluid-suppressed T2 contrast (FLAIR SPACE; "3D FLAIR MS-P") and a 3D T1 contrast (MPRAGE; "3D T1 MS-P") for detection of changes in T2 lesion burden and brain volume (for protocol details, see Table 1).

These two contrasts are taken as input for generating the imaging biomarkers (most importantly NET2L and BPF change) needed for the assessment. The lesion segmentation is a novel, fully automated prototype software, which showed good robustness and detection performance both cross-sectionally and longitudinally since it also takes partial volume effect into account [11–13].

During the development of MSPie, the BPF calculation was highly optimized in order to be able to robustly measure smallest volume changes, as the average rate of brain atrophy in MS is only about 0.5%/year.

The *syngo*.via Frontier setup is configured to allow an automated routing of the sequences described in Table 1 to *syngo*.via which then retrieves the prior MRI (if available) from the PACS and sends it to MSPie. The images are immediately analyzed and results are available approximately 10 minutes after the acquisition without any user interaction. They can then be viewed and evaluated in a graphical user interface (GUI) which was specifically designed for the application in the MS PATHS centers. The experiences gathered during its design and optimization in the clinical testing workflow were incorporated into the reports which are output by the product solution.

The MSPie GUI consists of two panels and a separate control area (Fig. 1). The main page provides the processed prior and current standardized "3D FLAIR MS-P" and "3D T1 MS-P" images overlaid with T2 lesions (blue) and whole brain parenchyma segmentations (green), respectively. A grey scale difference map presents highlighted changes over time accompanied by a color-coded map, where new or enlarging T2 lesions are marked differently (red) from stable lesions (blue). NET2L volume, total T2 lesion volume, T2 lesion volume fraction per total brain volume as well as the sub-volumes of juxtacortical, periventricular, infratentorial, and remaining other lesion types are provided together with their percentage change since the prior MRI.

2 The automatically generated report contains all the quantitative metrics displayed in the user interface. Subdivided into T2 lesion metrics and morphometry, i.e., volume measurements, the aim was to create an overview to inform referring neurologists of processing and evaluation results. Supplementary information documents technical constraints and quality impairments.

Brain volume is provided as BPF, alongside with the segmented grey matter (GM) and white matter (WM) fractions and their percent change. Additionally, volume fractions of cortical and deep GM and of the thalamus are generated.

The separated control area allows the evaluating neuroradiologist to edit the detected NET2L separately, i.e., NET2L can be removed from the results or added in case they were missed. In the latter case, a single click on the missed lesion is sufficient to activate a local segmentation, thus no manual segmentation needs to be conducted. In addition, both qualitative dials describing total lesion volume and BPF severity are provided based on a comparison with MS patients collected within the MS PATHS network.

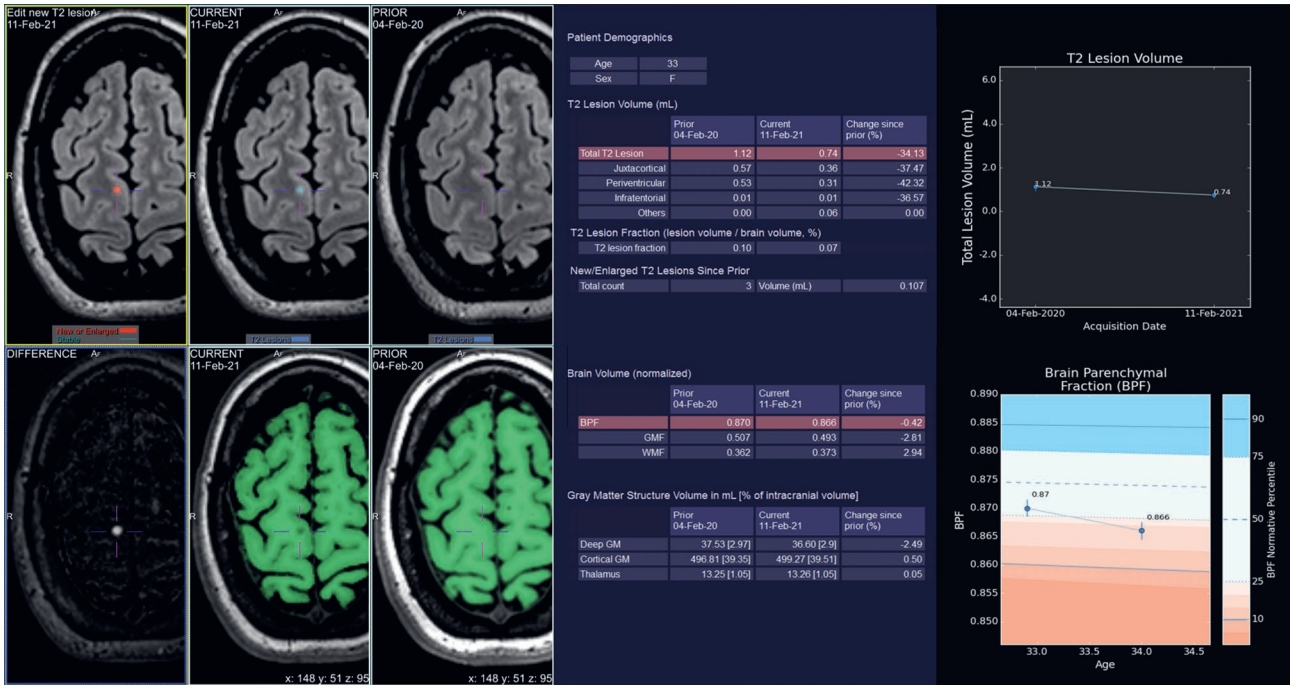
All results are included in the report (see Fig. 2) to inform on the quantitative analysis. The report is created only after completion of the interactive review and, if the results are accepted by the neuroradiologist, it is sent to the PACS to accompany MSPie annotated lesion and brain masks.

Results

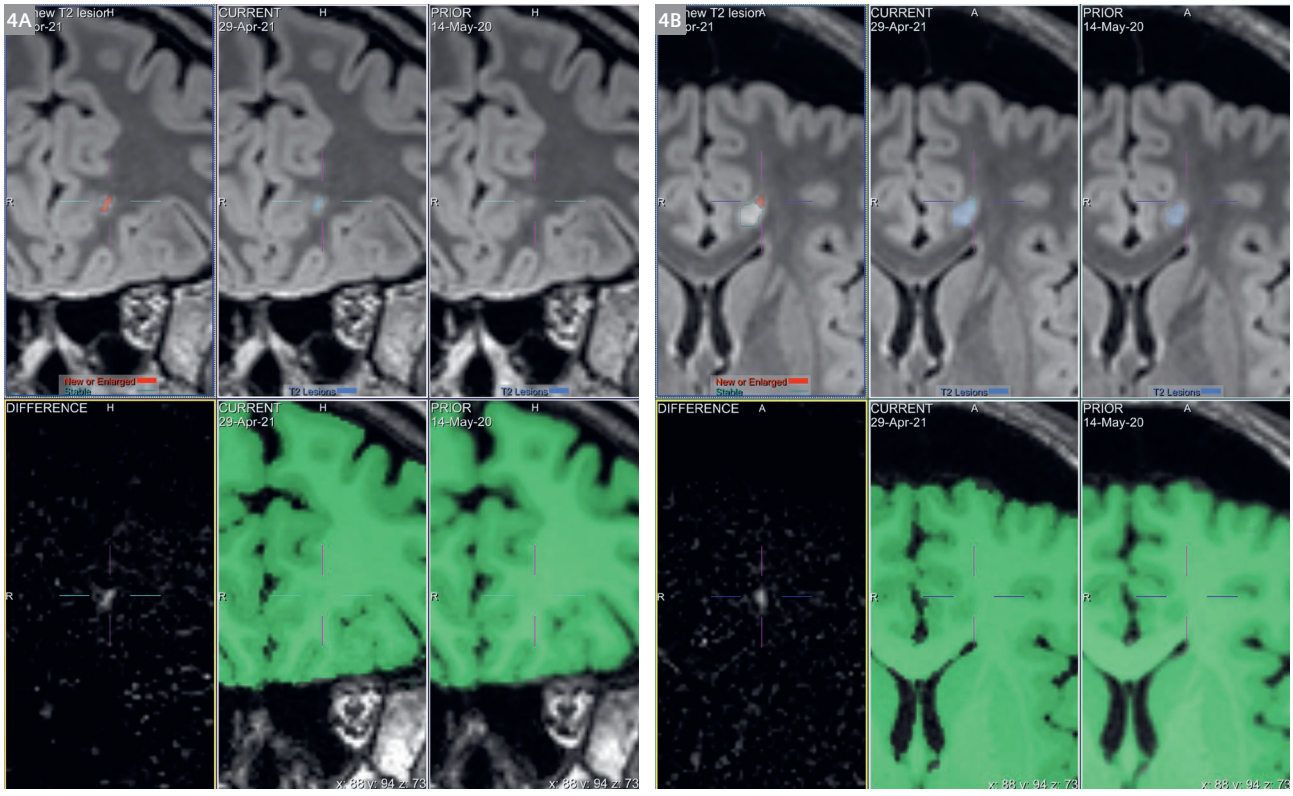
MSPie deployment into the MS radiology workflow

At our institution, we established an exploratory workflow to evaluate the integration of such a solution in our routine work while it was made sure that the standard radiological reading was not affected. The integration required minor adaptation of the institutional radiology workflow for follow-up MRI evaluation. For comparison with the MSPie results, the 3D FLAIR and T1 sequences were simultaneously reviewed in at least two perpendicular reformats in conventional setup. Furthermore, registered T2 and proton density acquisitions of the institutional protocol allowed infratentorial constraints of the 3D FLAIR-based lesion segmentation to be overcome. Reading using the MSPie prototype was arranged to follow conventional visual evaluation to avoid over-reliance on technical processing.

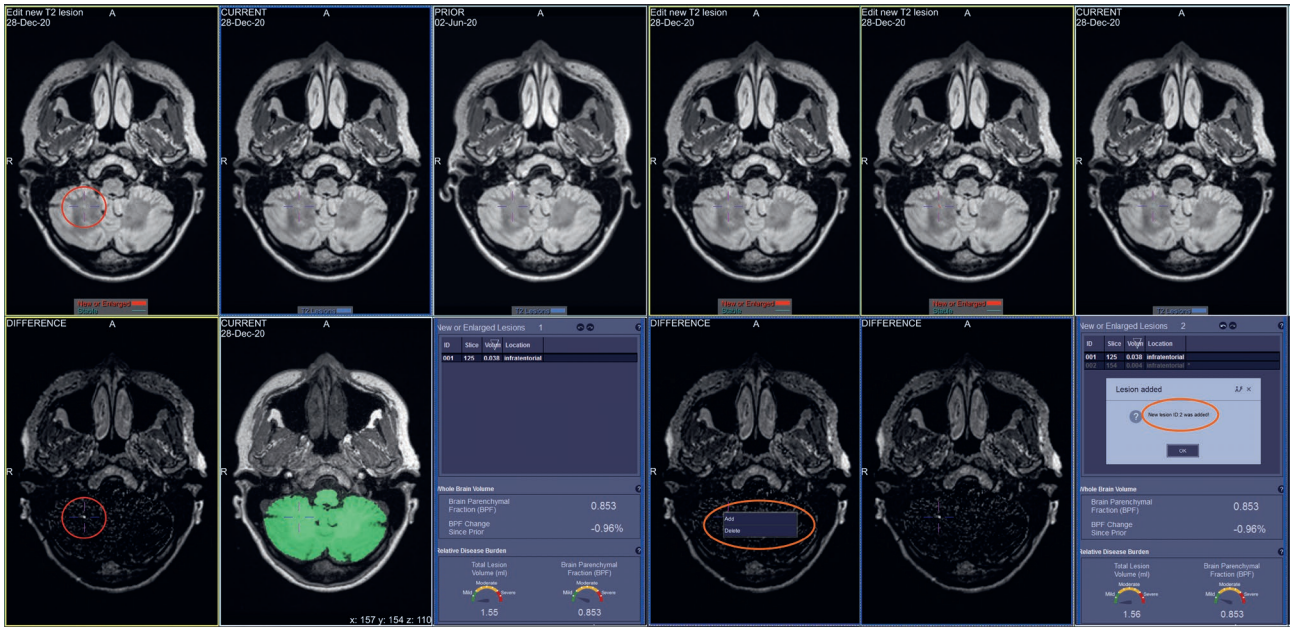
Since the MSPie evaluation was an additional procedure step of the application it initially prolonged the workflow. Whereas getting used to the MSPie handling compensated and subsequently even increased evaluation speed, some delay persisted in conjunction with institutional information technology performance restrictions. With growing confidence in the algorithm performance, we anticipate that evaluations can considerably accelerate today's routine reading.



3 Within the standardized annual follow-up examination of this example MS patient a new juxtacortical T2 lesion appeared in the right frontal location (crosshairs), visible in the difference map and classified as NET2L (red) in the upper left segment used for lesion editing. In this segment, lesions can be deleted or added if necessary (see Fig. 4).



4 Two example patients with lesion growth of different geometry in standardized follow-up examination. The volume increase can be quaquaversal, i.e., resulting in a volume inflation in all directions **(4A)**, but more often regional outgrowth can be detected **(4B)**, resulting in an annex exceeding the prior lesion boundary.



5 The MSPie prototype allows corrections to the automatically detected new or enlarging lesions. The difference map visualizes highlighted changes that occurred between the two time points (red circle; left half of the panel). Missed NET2L can be selected by an interactive window (orange ellipse) to add it to the NET2L segmentation.

Automated detection of new or enlarging T2 lesions

The detection of NET2L represents the essential task of the MRI evaluation in MS neuroradiology. Optimal MRI acquisition quality is thereby crucial to enable high precision of visual inspection. However, in MS patients with high lesion load, or with very small lesion size, juxtacortical lesions, or new lesions located adjacent to pre-existing lesions, visual detection can be challenging. Computer-assisted detection ensures high precision of the evaluating neuroradiologist even in difficult cases.

The software immediately provides all detected lesion differences with a clear visualization of stable lesions and NET2L volumes using well-distinguishable color-coding. Upon completion of conventional visual evaluation, it allowed checking for completeness, i.e., the review of perceived NET2L and other changes. This double-pass approach likely increases diagnostic certainty.

Besides newly forming lesions, lesion growth is also common in MS. Detection of enlarging lesions represents the more difficult task for the evaluating neuroradiologist since growth can be subtle, of complex geometry or ill-defined margins, and the surrounding diffusely abnormal WM might obscure the lesion formation and size change. However, lesion growth provides an important marker of subclinical inflammatory activity. The detection rate of enlarging lesions using conventional visual evaluation is therefore relatively low in comparison to new T2 lesions.

As with any image analysis software, automated lesion segmentation and change detection are subject to error. The interactive review of MSPie results was therefore deemed a significant feature when the prototype was in its planning stages. Thus, within MSPie, lesions missed (false negatives) and falsely detected NET2L (false positives) can be added or deleted using single mouse clicks in the GUI prior to being stored in the PACS or patient medical record (see Fig. 5). The generated corrections were consecutively used to optimise the final, non-interactive product solution.

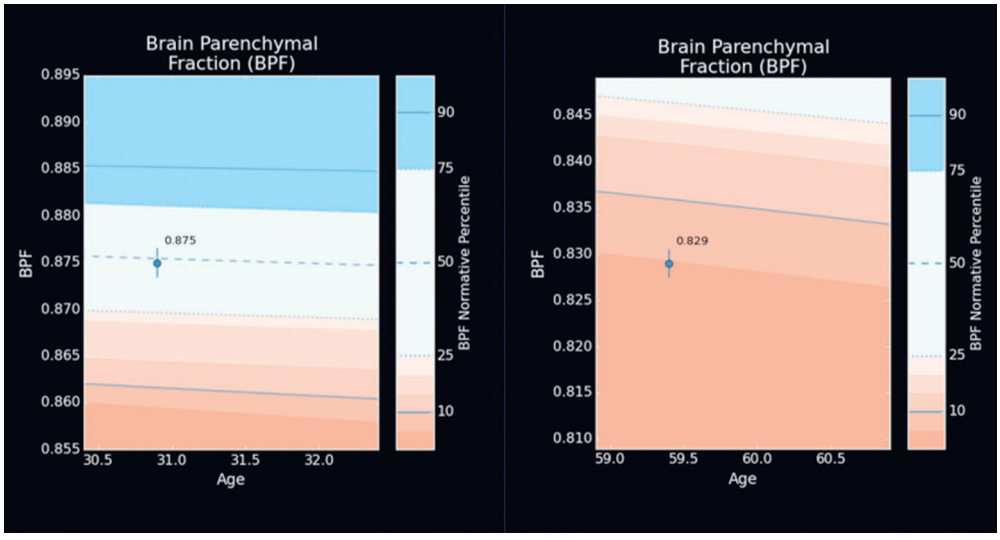
Upon finalization of the editing process and completed PACS archiving, all results are summarized in an embedded report (see Fig. 2).

Brain volume assessment

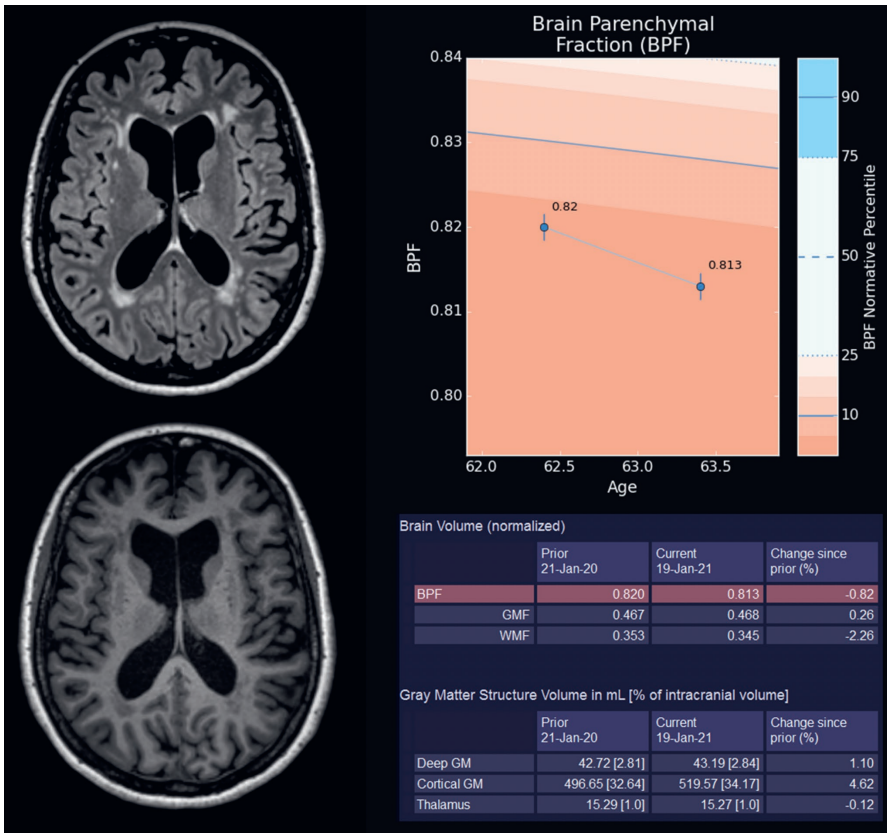
In later adulthood, continuous decrease of brain volume is observed in normal aging. In MS, brain volume loss, or brain atrophy, begins at disease onset and progresses at an accelerated rate compared to healthy controls throughout the disease course. Within MS PATHS, normative values for the BPF were established, which allow volumetric changes exceeding normal brain aging to be detected.

In the prototype software, the BPF is automatically calculated and plotted against an age-matched healthy control subgroup which indicates age-specific percentiles. This already allowed visual perception and immediate age-appropriate and age-inappropriate classification for a single time point (see Fig. 6).

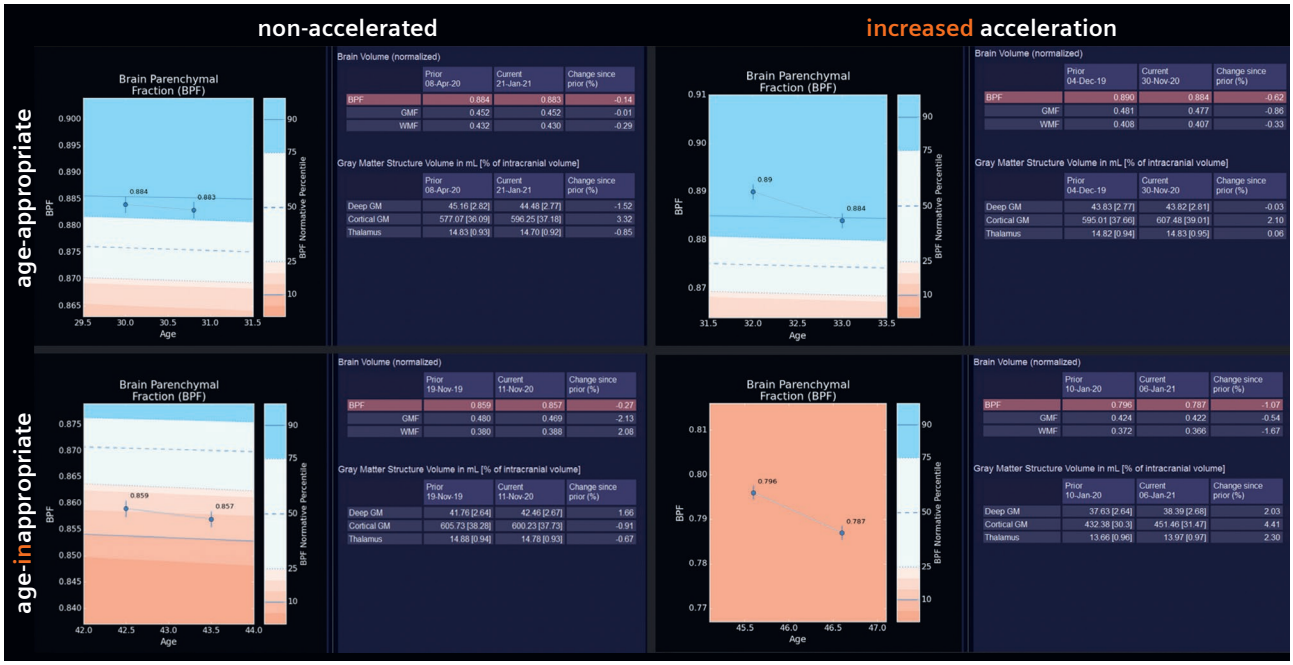
Further details of brain parenchyma volumes are provided, i.e., the normalized GM and WM volume fraction, as well as the compartmental volumes of cortical, deep and thalamic GM, including their shares in overall brain tissue volume.



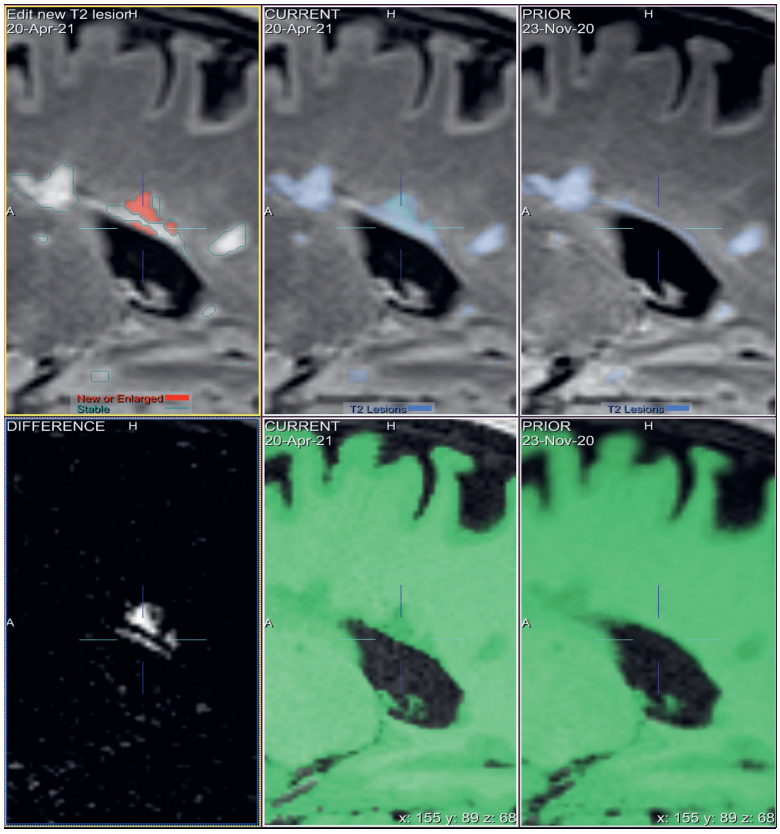
6 Cross-sectional evaluation to classify age-appropriateness of brain tissue volume for a given examination age using BPF percentiles. For quick reference the color-coded percentile score is displayed beside each plot for contextualization. Whereas the left case showed an age-appropriate BPF of 0.875 at the age of approx. 31 years, the right case clearly demonstrated an age-inappropriate BPF of 0.829 at the age of 59 years.



7 The natural course of MS is characterized by an accelerated loss of brain parenchyma resulting in age-inappropriate brain volume denominated as atrophy. The transition from age-appropriate to age-inappropriate normalized brain parenchyma volumes (BPF) is depicted in Figure 2. In the example on the left, BPF was already age-inappropriate at the prior MRI and further decreased by 0.82% in the annual follow-up, illustrating an explicitly increased acceleration of brain volume loss over time. The example FLAIR and T1 reformats below corpus callosum level visually demonstrated a predominant WM loss numerically confirmed by a relative 2.26% decrease.



8 A classification in categories attempt of MS brain volume conditions and slopes of parenchymal volume loss.



9 Multifocal growths of a stable periventricular lesion resembling three different NET2Ls selected by the prototype but effectively being separate growth zones of the same lesion.

Assessment of annual normalized brain volume change
To determine brain atrophy at the point of care in individual MS patients, the combined assessment of current state and rate of change is necessary. Based on the approach seen in Figure 8, four different descriptive classifications can be distinguished:

1. Age-appropriate and non-accelerated,
2. Age-inappropriate and non-accelerated,
3. Age-appropriate and increased acceleration, and
4. Age-inappropriate and increased acceleration, of BPF and BPF annual change, respectively.

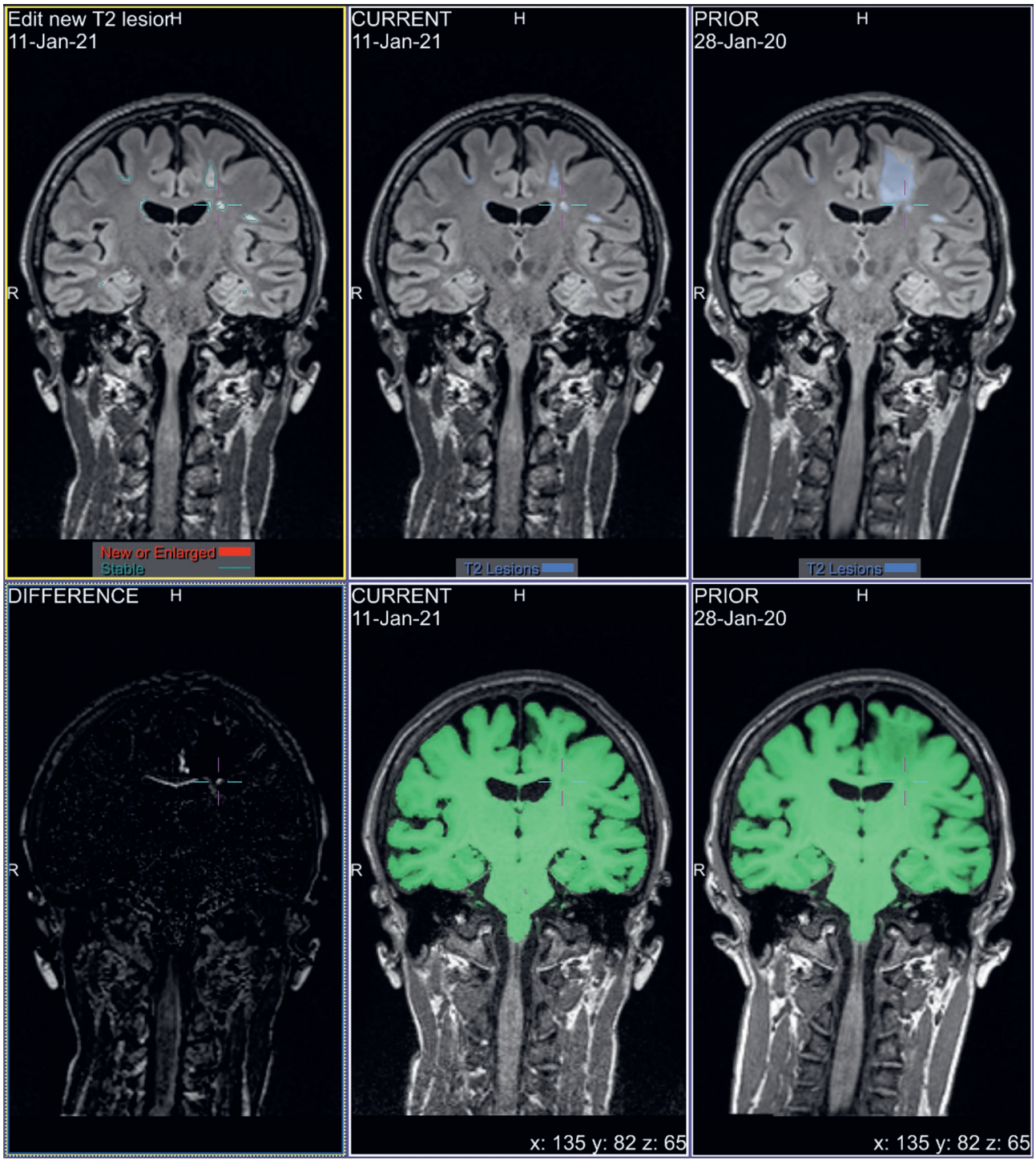
It should be noted that the normative data for the BPF change over time are generated from single-time point assessments; it is thus assumed that the resulting rate of change describes healthy brain aging accurately on a group level.

Perils and pitfalls

The evaluation of the well-defined new T2 lesion segmentation results did not represent a problem. A couple of conditions, however, require careful interpretation of computer assisted tools for MS.

First, new MSPie users had to become acquainted with assessing lesion growth, especially in confluent lesions. If lesion/conglomerate growth was multifocal, as is shown in an illustrative case in Figure 9, NET2L segmentation resulted in multiple separated growth areas, i.e., erroneously classified growing lesions. Hence, the NET2L number was artificially increased. More sophisticated editing is currently being discussed to mitigate this issue in future software versions.

The change of a stable lesion location between two consecutive scans due to temporary displacement led to anomalous segmentation. Since only growth but not shrinkage was detected, this resulted into erroneously classified lesion growth (Fig. 10).



10 Due to a left frontal hyperacute lesion with perifocal edema and swelling, an adjacent lesion (crosshairs) was displaced in the prior scan. When edema and space occupation are resolved in the current scan this lesion held a slightly different position (note the shift within the cross hairs). As a result, a difference due to the lesion position change was detected during follow-up of this, in fact, unchanged lesion.

11 A case of long-standing Baló's sclerosis with clinical progression. No new or growing lesions were found, but there was an annualized 1.87% BPF change. Since the absolute T2 lesion volume decreases, such extreme atrophy may result in concomitant total apparent lesion volume reduction.

The quantification of the T2 lesion burden and brain tissue loss may also not be independent from each other, since in severe atrophy, an apparent overall T2 lesion volume reduction may emerge, as observed in Figure 11. However, this issue might be expected in severe and predominant WM atrophy only, but may be overcome by correction.

Finally, co-morbid diseases in MS patients may complicate both conventional and computer-assisted image evaluation. The cause of possible confusion is the limited specificity of the T2 signal and lesions. Stroke residues, brain tumors, and post-traumatic gliosis (see example in Fig. 12) may resemble lesions detected by the prototype. To prevent erroneous inclusion, the respective patients need to be evaluated with caution to exclude all non-MS pathology in computer-assisted segmentation.

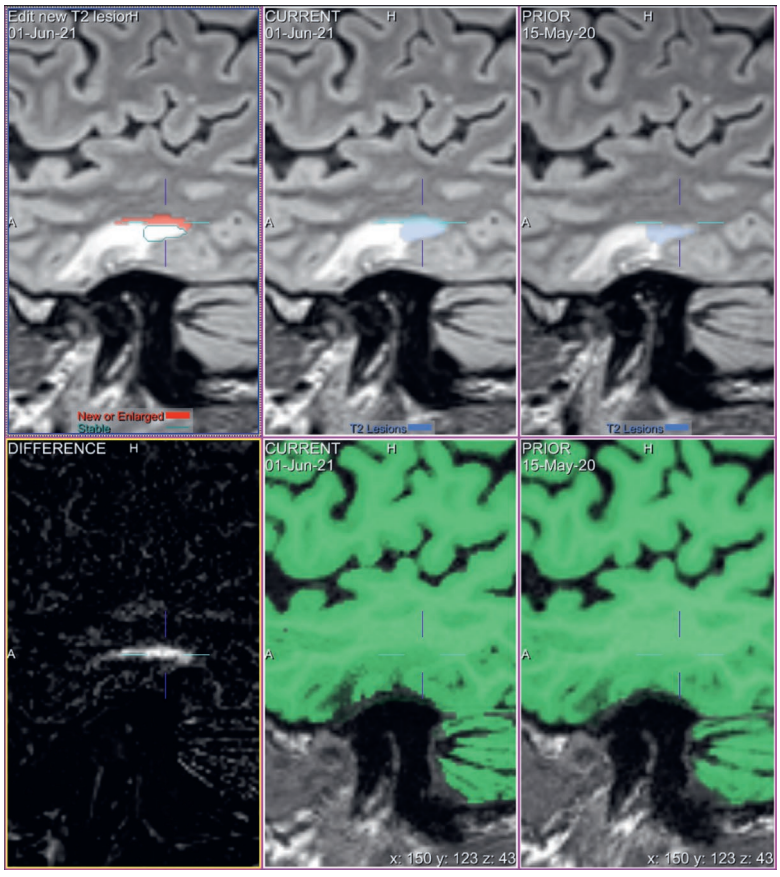
Discussion

MSPie provides automatic data routing, longitudinal processing, and visualization of the results, as well as report generation, integrated into the neuroradiologist's workflow. The immediate, automated analysis represents the most important development for efficient translation, since results are ready for evaluation promptly after the acquisition. Retrieving results directly after scanning will allow the integration into standard radiological reporting that immediately follows. For the evaluating neuroradiologist it can increase reading speed for most MS cases.

The integration of quantitative cross-sectional and follow-up information on imaging MS pathology, including NET2L and brain atrophy rates, in so-called subclinical disease activity monitoring after definite clinical diagnosis and under treatment, fulfills an increasing demand for translation of highly specific volumetric assessments to routine reading by treating MS neurologists [3, 6].

To achieve precise volumetric measurements and especially reliable assessments of their change over time, the standardization of imaging data acquisition is mandatory [14]. This was recently reiterated in recommendations on the use of MRI in patients with MS, with a particular focus on follow-up MRI protocols in established disease and under immune-modulating treatment [5].

Based on our preliminary experience, this software can provide distinct benefits for MS image evaluation precision and reliability. In MS cases with extensive MRI pathology, visual evaluation can be laborious and prone to neurora-



12 Post-traumatic temporal gliosis in an MS patient analyzed with the software prototype. The residue of a contusion resembles a T2 signal similar to an MS lesion and therefore was partly segmented. Progressing within the observation period, the prototype even detected lesion growth. However, this lesion needed to be excluded from the analysis.

diological misjudgment. Here, MSPie may ensure precision for follow-up MRI reading.

In particular, the MS imaging feature of subtle T2 lesion growth has likely been missed by conventional visual evaluation without computer aid. Hence, the importance of precision increase in clinical follow-up is obvious. However, this also identifies the need of common definitions of variants of MS lesion growth which are so far not incorporated into the neuroradiological repertoire of disease-related changes in MS [15].

The longitudinal quantification of brain tissue volume in MS allows the observation of increased rate of brain volume loss, exceeding the age-dependent acceleration. So far, conventional neuroradiology has been unable to quantify this characteristic feature of MS pathology in routine assessment. Thus, the precise determination of accelerated atrophy rates here appears to be the greatest translational advancement achieved.

However, the still incomplete clinical definition of MS imaging surrogates of subclinical disease activity and their clinical meaning [16, 17] presents neuroradiologists with a situation where precise characteristic alterations are provided at the diagnostic point of care that are still subject of debate in clinical MS neurology [18, 19].

Conclusions

Automated quantification of MS imaging metrics has long been a challenge, and the lack of standardization and highly precise techniques hindered its translation into clinical care. Insufficient MRI data quality, resolution, and limited reproducibility further impeded such application at the diagnostic point of care.

In combination with a perpetual standardized MR imaging protocol, the prototype may enable robust and fully integrated assessment of MS cases. While the neuroradiologist must remain vigilant with respect to machine-generated results, the software proves to support advanced clinical care and could serve the high information demand in MS neurology.

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