Update on FLAIR Fusion in Multiple Sclerosis Follow-up and Beyond: An Indispensable Tool in Clinical Routine

Andreas Bartsch, M.D.[1]; Thomas Illigen[2]

[1]Radiologie Bamberg, Germany
[2]Siemens Healthineers, Erlangen, Germany

This is an update on the article "FLAIR Fusion in Multiple Sclerosis Follow-Up: An Indispensable Tool in Clinical Routine" by Stéphane Cantin and Emeline Lamain (Groupe Clinique du Mail, Grenoble, France), and Thomas Troalen and Melisa Bakir (Siemens Healthineers, Saint-Denis, France) that was published in ↗ MAGNETOM Flash (69) 3/2017.

Background

Modern radiologists face the challenge of managing a rising number of examinations (which, with more focus on 3D imaging and multiplanar reconstructions, themselves include an increasing number of images) without compromising the quality of their reports. *syngo*.via offers solutions to meet this challenge.

Radiologie Bamberg is a German radiological practice with a focus on neuroradiology and inflammatory CNS diseases like multiple sclerosis (MS), in particular. Its MR scanner primarily used to address the related clinical-radiological challenges is a 64-channel 3T MAGNETOM Skyra, now running on Numaris X with software version *syngo* MR XA30. Established core brain MR recordings for monitoring MS are a sagittal 3D FLAIR at 1 mm isotropic resolution or sagittal and axial 2D FLAIR at 3 mm slice thickness and submillimeter in-plane resolution.

For follow-up studies and comparisons, we generally recommend and use the AutoAlign functionality, since it is very beneficial for recording subsequent studies in good initial alignment, especially if anisotropic 2D recordings are used.

Follow-up of MS patients primarily consists of comparing current and prior examinations. The European Collaborative Research Network Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS), has – together with the Consortium of Multiple Sclerosis Centers (CMSC) and the North American Imaging in Multiple Sclerosis Cooperative (NAIMS) – just recently published consensus recommendations on the use of MRI in MS [1], both for establishing the diagnosis and specifically for longitudinal follow-ups and monitoring the effectiveness and safety of treatment. To support detection of new MS- or treatment-related progressive multifocal leukoencephalopathy (PML) lesions, *syngo*.via can be used.

Inspired by the article "FLAIR Fusion in Multiple Sclerosis Follow-Up" by Stéphane Cantin, Thomas Troalen, Emeline Lamain, and Melisa Bakir published in MAGNETOM Flash 69 [2], we introduce further modifications, improvements and simplifications to the workflow and extend it to other applications, such as the detection of T2-progress in gliomas.

Goals

Using the previously described MPR/MPR overlay and the parathyroid-blue Color look-up table (LUT) recommended by Cantin et al. we were able to replicate their identification of new lesions. Yet, our goal and purpose for further development and improved *syngo*.via application was

1. to fully meet and comply with the new 2021 MAGNIMS-CMSC-NAIMS recommendations, which emphasize the clinical utility of co-registration, fusion, and subtraction techniques, especially if T2 lesion load is high and to increase the sensitivity for detecting new T2 lesions [1] (Panel 4, p. 10 and Appendix p. 7);
2. to provide a visualization of the registration quality between successive scans (prior and current) for QA/QC purposes; and
3. to enable the (neuro)radiologist to clearly differentiate between
   a) new or progressive lesions;
   b) unchanged lesions ("no evidence of disease activity" = NEDA according to radiological criteria);
   c) potentially decreasing lesions,

not only in MS, based on the information we can extract from the MR images.

Method

Evaluation of intramodal registration quality, see above, is essential for QA/QC in serial assessments because even at the same scanner and coil, using the same software and sequences, image co-registration/fusion is never perfect. In theory, intra-individual image registration upon follow-up is an affine problem requiring six (three translations and three rotations, "rigid-body co-registration") or seven (+ global scaling) degrees of freedom (DoF). However, gradient nonlinearities and image distortions pose challenges for this model and may lead to suboptimal results after image registration. Naturally, registration accuracy tends to be more limited for anisotropic 2D than isotropic 3D recordings, but 3D pulse sequences are more vulnerable to image intensity variations across the acquired volume. Notably, the quality of image registration between current and prior scans will influence both the sensitivity and specificity for detecting changes in lesion load or volume. Sufficient image registration accuracy is currently one of the main obstacles limiting the technological availability and widespread use of serial subtraction scans for MS follow-up, treatment, and pharmacovigilance safety monitoring as recommended by the 2021 MAGNIMS-CMSC-NAIMS consensus. Another main challenge is, due to the non-quantitative nature of standard scans, to achieve a common image intensity scaling to a best denominator between previous and follow-up scans.

We relinquished the use of color overlays as proposed by Cantin et al. and instead use an inverted grayscale. Numaris X software now provides *syngo*.via functionalities also on the scanner. One benefit is the automated grayscale adaption with no need for individual windowing using the MPR/MPR overlay, especially with the images from the prior examination being displayed at inverted grayscale on top of the current scans. The idea behind this approach was to

a) highlight new lesions,
b) obscure those that did not change in comparison and
c) obtain opposed contrast to a) for areas that decreased in size.

The latter and QA/QC evaluation of the image registration quality is not sufficiently feasible using color volume overlays.

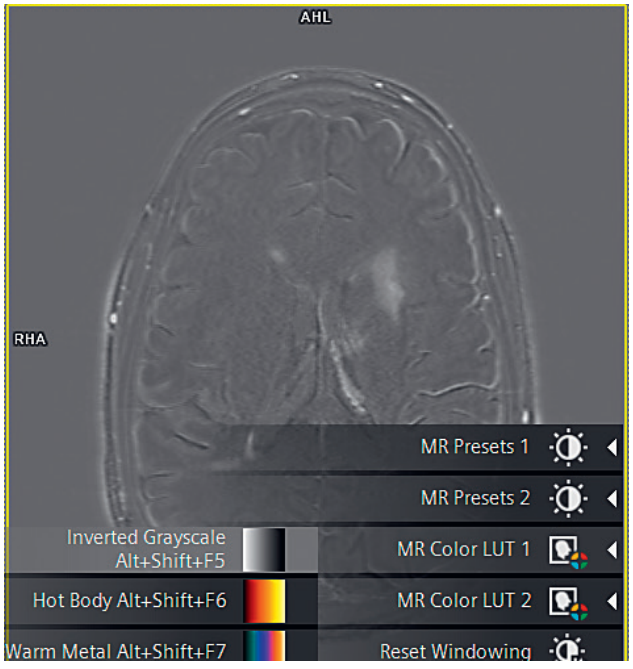
Workflow

To establish our new workflow on *syngo*.via or directly on the scanner in View&GO, you need to simultaneously load the current and prior examinations. This can be achieved automatically with *syngo*.via using the prefetch functionality.

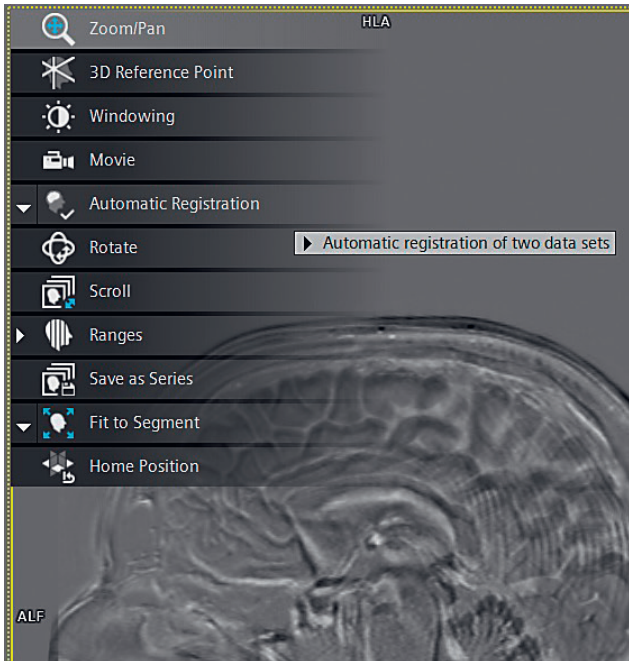
We would recommend a 2 x 3 layout to display the images in axial and sagittal orientations. Depending on your examination strategy and/or monitor settings, other layouts might be more expedient.

As a next step, an MPR/MPR overlay is created as described by Cantin et al.

For the reasons detailed above, we do not use the parathyroid-blue Color LUT. Instead, we recommend using the inverted grayscale overlay, which effectively yields an intensity-normalized subtraction between the current and



1 Assigning the MR Color LUT 1 Inverted Grayscale.



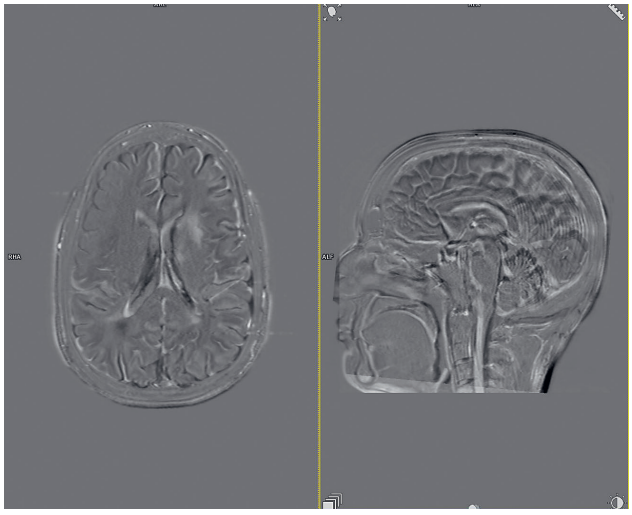
2 Top-left menu with Automatic Registration tool.

prior examination. Please note that Color LUT 1 will be used for the second loaded dataset; usually this will be the prior examination (Fig. 1).

It is essential to co-register the datasets. The Automatic Registration tool can be used for this next step.

The automatic registration is applied for all datasets simultaneously, so axial and sagittal images will be coregistered together just with one click.

Automatic registration will only work if both the current as well as prior exam have either been distortion corrected or not. We recommend 2D distortion correction per default. However, if this was disabled for one of the exams it can be reset in syngo.via for the other to generate a new series to match the two for registration.



3 Axial and sagittal MPR/MPR inverted grayscale overlays before co-registration.*
** Although the initial overlay is reasonable, due to AutoAligned acquisitions, it should be further improved.*

If the automatic registration should not meet the expectations, there is still the opportunity to perform a visual alignment or manual registration of the two datasets (Fig. 5).

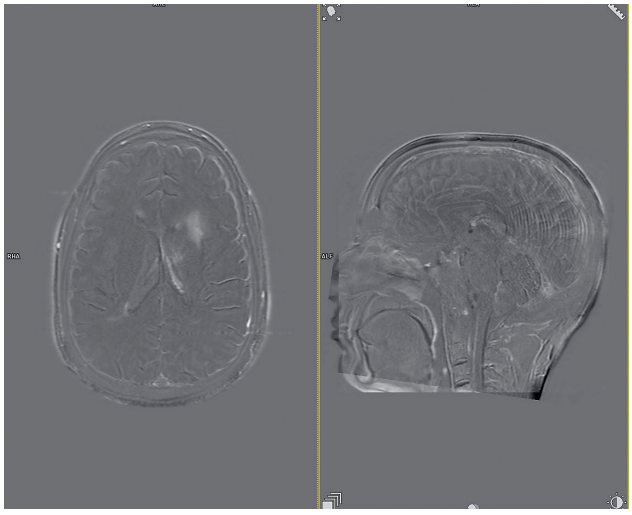
The proposed layout now offers, at rapid and convenient glance, a fast and easy comparison and reliable appraisal of lesions according to our primary goals a) to c) (see above).

The arrows and arrowheads in Figure 6 mark new FLAIR-hyperintense lesions in the current dataset as compared to the previous examination. The MPR/MPR overlay of our workflow properly highlights those lesions as white hyperintense areas at high contrast.

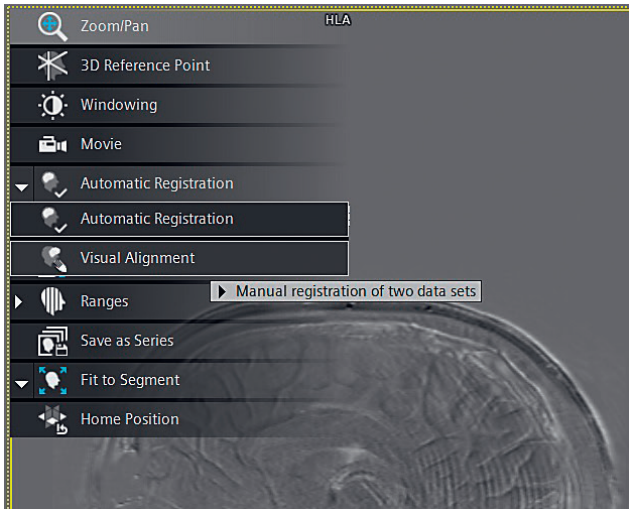
The red arrow in Figure 7 depicts an unchanged lesion in the current as compared with the previous examination. It is "zeroed out" in the MPR/MPR overlay, confirming that there is no radiological evidence of disease activity with regards to this particular lesion.

The following slice from another case in Figure 8 shows the conceivable lesion behavior of new or enlarging, unchanged, and decreasing lesions all in one image.

On the slice from the current data, the red arrow indicates an unchanged lesion which is "zeroed out" in the overlay subtraction (right), while the pink arrow reveals a new, expanding lesion juxtacortical to the insular cortex. The green arrow on the slice of the prior examination shows a lesion that was decreasing in the current compared with prior examination and which is visualized hypointense (black) on the MPR/MPR overlay.

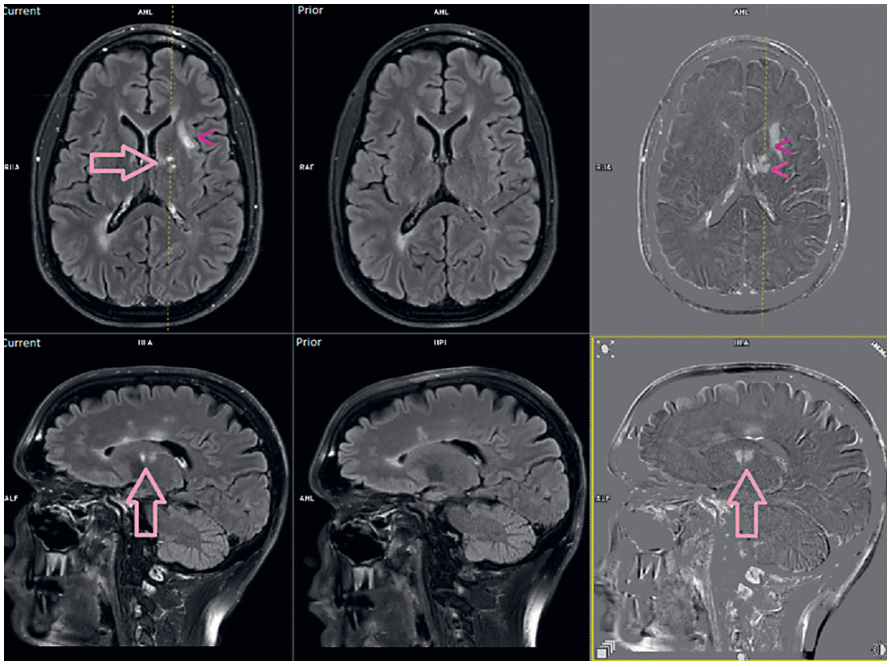


4 Axial and sagittal MPR/MPR inverted grayscale overlays after automatic registration.*
** Better (though not perfect) alignment between the current and prior scans becomes obvious at the outer and inner (ventricular) brain edges.*

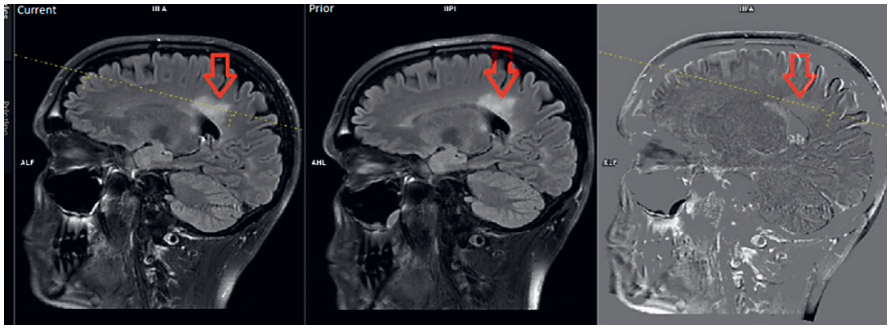


5 Top-left menu with Visual Alignment tool.*
** In our experience, a visual alignment was never necessary; automatic registration is recommended.*

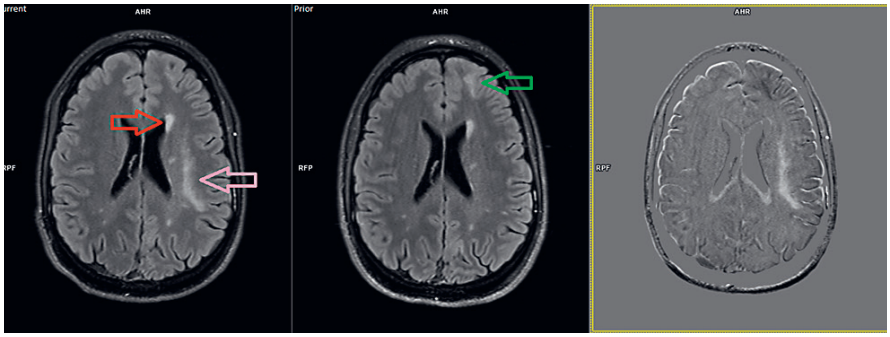
Registration accuracy is best judged on the outer and inner (ventricular) brain edges. Here, misalignments will show up as hyper- and/or hypointense bands, respectively, in subtraction images. Such misalignments also affect the appearance of lesions in the overlay images and can, if not judiciously accounted for, lead to false-positive and false-negative detections. Compared to color overlays, our use of an inverted grayscale in a 2 x 3 layout substantially facilitates the recognition of such registration errors and thereby enhances both sensitivity and specificity.



6 Detection of new lesions upon MS follow-up according to our workflow.*
** Note that for the current but not prior examination, gadolinium agent has been applied IV before the FLAIR acquisitions to prolong the delay to improve contrast enhancement as per the latest MAGNIMS 2021 recommendations. Therefore, there is positive contrast in the overlay subtraction images on the right in the choroid plexus.*



7 Concealing unchanged lesions upon MS follow-up in our workflow.*
** Also note the regression of mucosal swelling in the maxillary sinus in the current as compared to the prior exam, which therefore shows up hypointense in the overlay subtraction image on the right.*



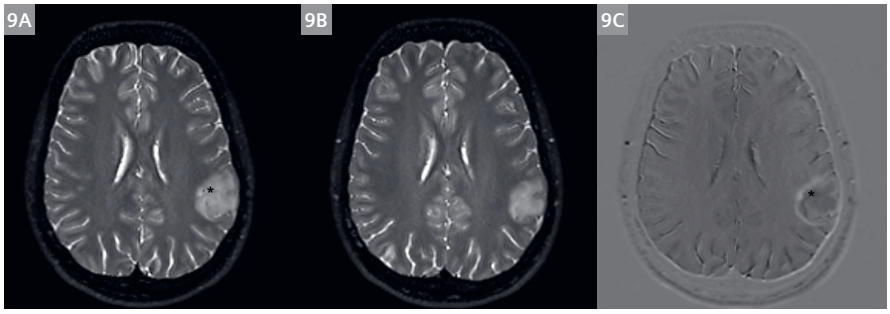
8 New (pink arrow), unchanged (red arrow), and decreasing (green arrow) lesions in a patient positive for the John Cunningham polyomavirus (JCV) with MS who developed an inflammatory PML after his 81st natalizumab infusion. Unchanged lesions are "zeroed out" in the MPR/MPR overlay, while new or enlarging lesions appear hyperintense, and regressive lesions hypointense. This is the desired behavior.*
** Slight misalignments between the current and prior scans appear as hyper/hypointense bands at brain edges and allow to assess the quality of image registration.*

In theory, optimal alignment of prior and follow-up scans would involve an unbiased, robust, inverse consistent co-registration into a mid-space between both images (in order to apply the same amount of interpolation to both) that iteratively deweights areas of high variance (i.e., differences/changes) between the two time points [3–5]. However, in our experience automatic registration of current and prior exams using MPR/MPR with inverted grayscale overlay works quite well if the same scanner and sequence were used for follow-up.

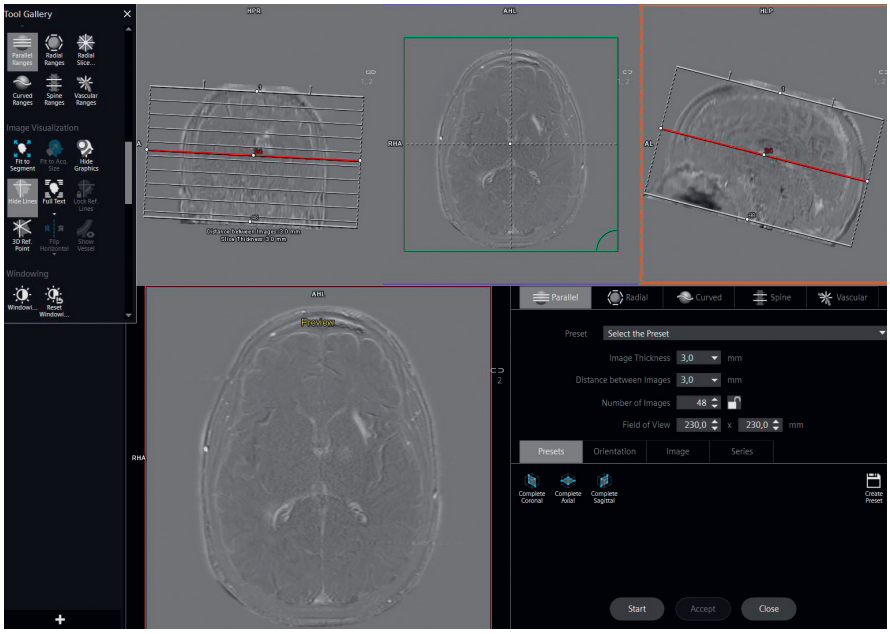
For 3D sequences recorded at 3T, particular care is required to avoid variable image intensity biases in the serial scans. If image alignment is sufficiently accurate according to visual QA/QC judgement, new lesions well below the 3 mm scale (reference size according to QBK-RL 2020 [6]) can be detected, in our experience even at the 1 mm scale.

Conclusion

In summary, our new proposed workflow enables the user to rapidly perform image co-registration, fusion, and intensity-normalized inverted grayscale overlay of serial scans that allows for good quality control and visualizes differences in lesion load/volume (i.e., numerical and in lesion extent) at opposite contrast while "zeroing out" unchanged



9 Detection of long-term T2 progression in a left supramarginal oligodendroglioma using co-registered 1 mm isotropic fat-saturated 3D T2 SPACE scan subtraction.
(9A) Current exam (March 2021).
(9B) Prior exam, not yet registered to (9A) but displaying approximately the same location at the tumor level, dating back 44 months (June 2017; and prior to stereotactic biopsy).
(9C) T2 scan subtraction using co-registered and inverted grayscale overlay of (9B) on (9A).



10 Axial reconstruction using the Parallel Ranges tool.

lesions as in subtraction images. This meets the recently published MAGNIMS-CMSC-NAIMS 2021 consensus recommendations on the clinical utility of co-registration, fusion, and subtraction techniques for monitoring disease activity, treatment response, and treatment safety in MS, especially if T2 lesion load is high, and to increase the sensitivity for detecting new T2 lesions [1].

According to in-house experience during the past year, our workflow may lead to several MS lesion detections which would have otherwise, due to high lesion load of the patient or, similarly, high work load of the reporting radiologist, been missed.

Furthermore, the technique can equally be applied to monitor T2 progress and treatment responses in intra-axial brain tumors, such as gliomas. In Figure 9 long-term, crescent-shaped T2 progression of the primary brain tumor became apparent comparing (Fig. 9A) and (Fig. 9B) and is accurately visualized in (Fig. 9C). Previously, it was missed on the short-term comparison of successive scans. The tiny dot (*) of a hypointense signal loss in the medial aspect of the tumor is due to a microbleed from the biopsy and also detectable on (Fig. 9C). The main tumor bed comes out slightly hypointense (i.e., with negative overlay values) due to discrete changes of the signal characteristics of the oligodendroglioma.

Additionally, any on a suitable given sequence/contrast hyper- (or even hypo-) intense lesion can be longitudinally monitored by our method (e.g., epidermoid cysts on diffusion or arachnoid cysts on T2/FLAIR) and, at least in theory, even the development of brain atrophy (which will present as “misregistration bands”; see OA/QC of registration accuracy in the Workflow section above). Global (and local) atrophy development is generally considered to reflect a neurodegenerative component of MS [7] but its assessment is not part of the current MAGNIMS 2021 recommendations [1].

For documentation and storage, the created MPR/MPR overlays can easily be reconstructed and saved in a separate series using the Parallel Ranges functionality (Fig. 10). To avoid interpolation artifacts, we recommend to reconstruct the subtraction overlays at no less than 2 mm slice thickness (we routinely use 3 mm). These subtraction series (“delta maps” or “change maps”) are then exported to the institution’s PACS.

The overlay subtractions generated by our workflow are – aside from pure radiological disease, treatment, and safety monitoring itself – well suited to present the detected changes to the patient in an intuitive manner that is easy to understand in order to argue for treatment options, to obtain informed consent, and to potentially improve compliance with the suggested management during further personalized care.

Acknowledgment

We are very grateful for the long-standing collaboration, support, and regular suggestions and requests for improvements provided by Dr. Boris-Alexander Kallmann, M.D., from the Multiple Sclerosis Center Bamberg (MSZB).

References

1 Wattjes MP, Ciccarelli O, Reich DS, Banwell B, de Stefano N, Enzinger C, et al. 2021 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. Lancet Neurol. 2021;20(8):653–670.
2 Cantin S, Troalen T, Lamain E, Bakir M. FLAIR Fusion In Multiple Sclerosis Follow-Up. MAGNETOM Flash. 2017;69(3):100–103. Available from https://www.magnetomworld.siemens-healthineers.com/clinical-corner/application-tips/flair-fusion-in-multiple-sclerosis-follow-up.html
3 Reuter M, Rosas HD, Fischl B. Highly accurate inverse consistent registration: a robust approach. Neuroimage. 2010;53(4):1181–1196.
4 Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage. 2012;61(4):1402–1418.
5 Reuter M, Gerstner ER, Rapalino O, Batchelor TT, Rosen B, Fischl B. Impact of MRI head placement on glioma response assessment. J Neurooncol. 2014;118(1):123–129.
6 Richtlinie des Gemeinsamen Bundesausschusses über Kriterien zur Qualitätsbeurteilung in der Kernspintomographie nach § 135b Absatz 2 SGB V [Internet]. Berlin, Germany: Gemeinsamer Bundesausschuss [cited February 10, 2022]. Available from: https://www.g-ba.de/downloads/62-492-2036/QBK-RL_2019-10-17_iK_2020-01-01.pdf
7 De Stefano N, Stromillo ML, Giorgio A, Bartolozzi ML, Battaglini M, Baldini M, et al. Establishing pathological cut-offs of brain atrophy rates in multiple sclerosis. J Neurol Neurosurg Psychiatry.2015;0:1–7.

Contact

PD Dr. med Andreas Bartsch, M.D.
Radiologie Bamberg
Heinrichsdamm 6
96047 Bamberg
Germany
bartsch@radvisory.net

Thomas Illigen
SHS EMEA CWE DI MR
Karlheinz-Kaske-Str. 2
91052 Erlangen
Germany
thomas.illigen@siemens-healthineers.com