# Synthesized
# Magnetic Resonance Imaging

# and
# SyMRI®

## Theory and Application

## A White Paper

Marcel Warntjes, PhD.

SyntheticMR

# Table of contents





# SyMRI® technical overview

## Synthesized MR image acquisition and reconstruction

Synthesized MR image acquisition and reconstruction holds great potential to reduce exam time, improve the patient experience, and bring novel diagnostic functionality and visual acuity to the reader.

It is based on absolute quantification of physical parameters of the patient that govern the image signal intensity in MRI, namely T1 relaxation, T2 relaxation and proton density PD.

Using these parametric maps, in combination with virtual scanner settings for echo time TE, repetition time TR and inversion delay time TI, conventional images, such as T1W, T2W and FLAIR images, can be synthesized. This means th at a whole range of conventional images can be reconstructed using a single quantification scan.

## SyMRI pulse sequence

The SyMRI pulse sequence is a 2DFSE multi-dynamic, multi-echo (MDME) sequence, which is performed using an interleaved slice-selective 120 degrees saturation and multi-echo acquisition. The saturation acts on a slice n, whereas the acquisition acts on a slice m, where n and m are different slices of the planned stack of slices. In this way the effective delay time between saturation and acquisition of each particular slice can be controlled by the choice of n and m.

There are four different choices of n and m performed (four dynamics), resulting in four different delay times (TI). This is done automatically and requires no user interaction. The number of echoes of the acquisition is fixed to two, at two different echo times. Hence the result of each MDME acquisition is 8 (complex) images per slice (4 saturation delays, at 2 echo times, see for example Fig. 1). More details on the sequence can be found in Warntjes et al. Magn Reson Med 2008:60;320-329.

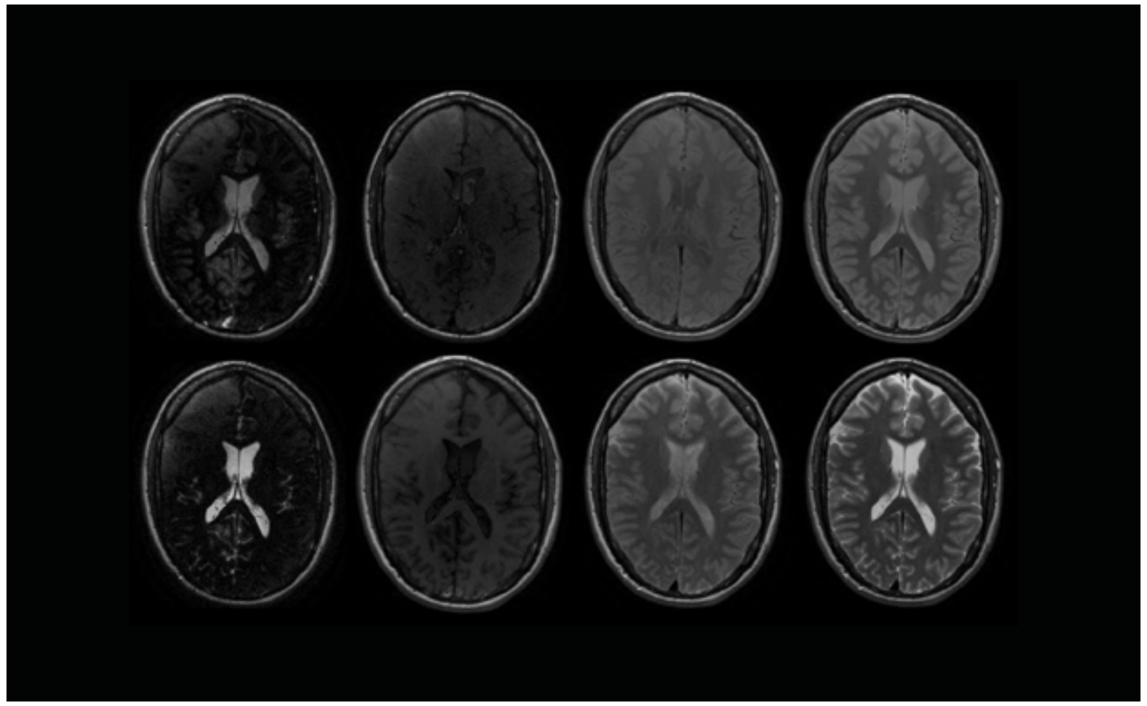

Fig. 1

Fig. 1. Raw MDME images of a single slice.
The images are complex and hence have a real and imaginary component.
Only the modulus ( sqrt(sqr(real) + sqr(imaginary)) ) is shown here.

## SyMRI® post-processing

The MDME images all exhibit different effects of the T1 relaxation time and T2 relaxation time of the imaged tissues. The SyMRI algorithm does a least-square fit on the signal intensity S of each pixel of the 8 images per slice and calculates the T1 and T2 relaxation values. Additionally it calculates the proton density PD and the amplitude of the B1 field according to:

$$S = A \cdot PD \cdot \exp(-TE/T_2) \cdot \frac{1-[1-\cos(B_1\theta)]\cdot\exp(-TI/T_1)-\cos(B_1\theta)\cdot\exp(-TR/T_1)}{1-\cos(B_1\alpha)\cdot\cos(B_1\theta)\cdot\exp(-TR/T_1)}$$

Eq. 1

where A is an overall intensity scaling factor taking into account the coil sensitivity, the RF chain amplification and the voxel volume, is the applied 90 degrees excitation flip angle and is the applied 120 degrees saturation pulse angle. An example of T1, T2, PD and B1 SyMaps™ are shown in Fig. 2. B1 is not shown to the user, since it has no clinical relevance. It is possible to show the relation rates as well, R1 (1/T1) and R2 (1/T2). The processing time is approximately 8 seconds.



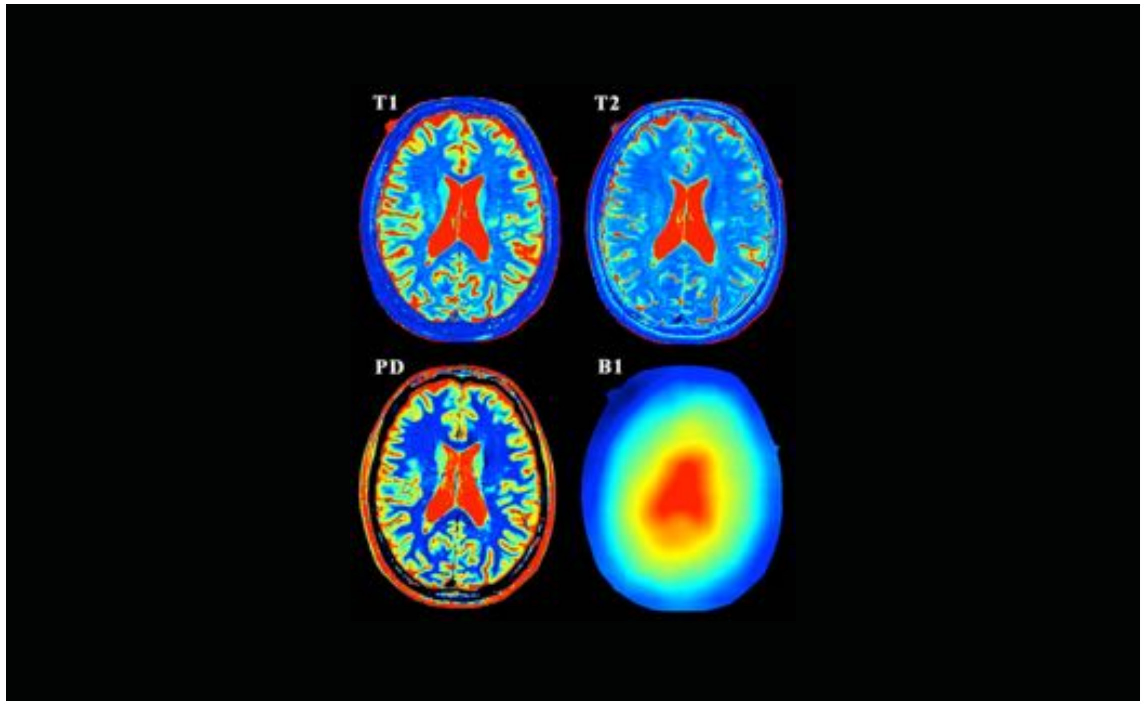


Fig. 2

Fig. 2. Processed MDME images, resulting in SyMaps of the T1 relaxation time, the T2 relaxation time, the proton density PD and the B1 field.

## Creation of synthetic images

Once T1, T2 and PD values are known normal MR images can be recreated, or synthesized, by calculating the expected signal intensity S, as a function of echo time TE, repetition time TR and, if applied, an inversion pulse with inversion delay time TI. The same Eq. 1 is used for this, where A is set to 1, B1 is set to 1 and is set to 90 degrees.

For T1-weighted and T2-weighted FSE images, is set to zero and Eq. 1 simplifies to:

$$S = PD \cdot \exp(-TE/T_2) \cdot (1 - \exp(-TR/T_1))$$

Eq. 2

For inversion recovery IR-FSE images, such as FLAIR, is set to 180 degrees and Eq. 1 simplifies to:

$$S = PD \cdot \exp(-TE/T_2) \cdot (1 - 2 \cdot \exp(-TI/T_1) + \exp(-TR/T_1)) \quad \text{Eq. 3}$$

In Eq. 3 the signal S can become negative. Typically, the absolute value is provided unless the user choses the 'PSIR' option, which keeps the sign.

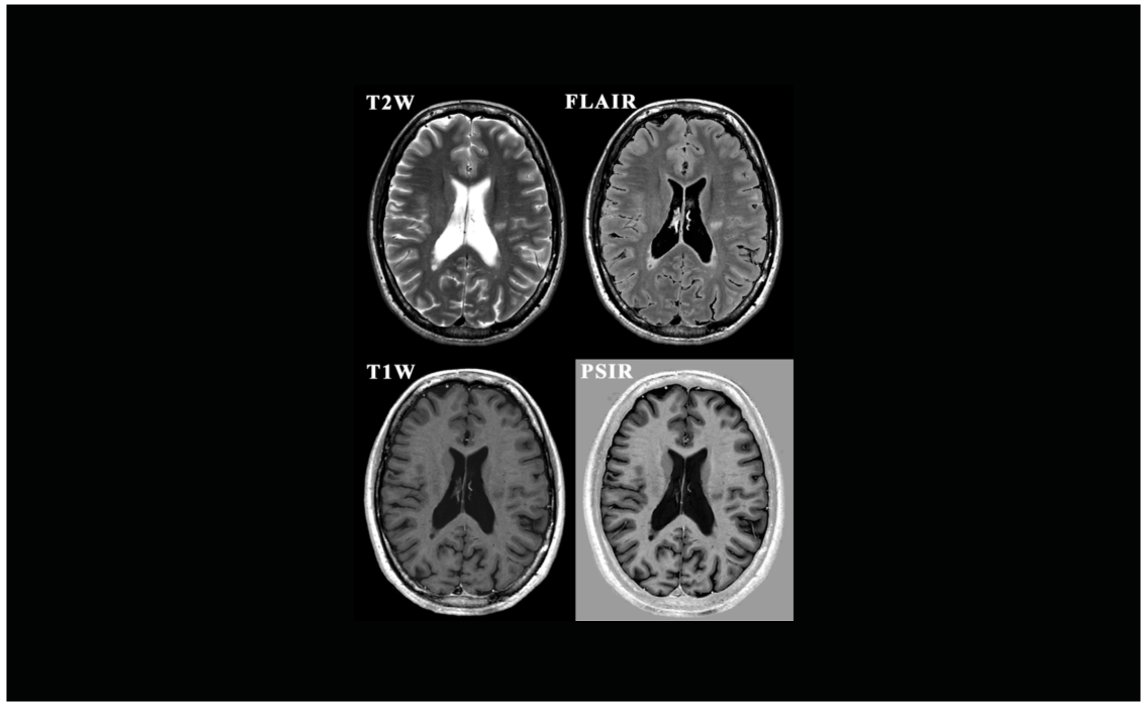


Fig. 3

Fig. 3. Examples of SyMRI®images, all based on the T1, T2 and PD maps of Fig. 2. There are FSE images such as T1W and T2W and IR-FSE images such as the FLAIR and PSIR images.



## Tissue segmentation

Instead of synthesizing MR images, the user can also display synthetic tissue segmentation maps based on the T1, T2 and PD SyMaps. White matter, grey matter, cerebrospinal fluid and myelin are automatically found. Also the intracranial outline is automatically determined. The segmentation is performed as a partial volume model, where each voxel in the stack can contain 0 to 100 percent of a specific tissue type. This makes the segmentation virtually independent of image resolution and angulation.

A User Mask is available where tissue can be copied, added and subtracted for further volume analysis of tissue of interest.

Tissue segmentation is important in the follow-up in neuro-degenerative diseases for objective decision making. Validation of the technique can be found in for example Ambarki et al, AJNR 2012:33;1951-1956 and Vågberg et al, AJNR 2013:34;498-504.

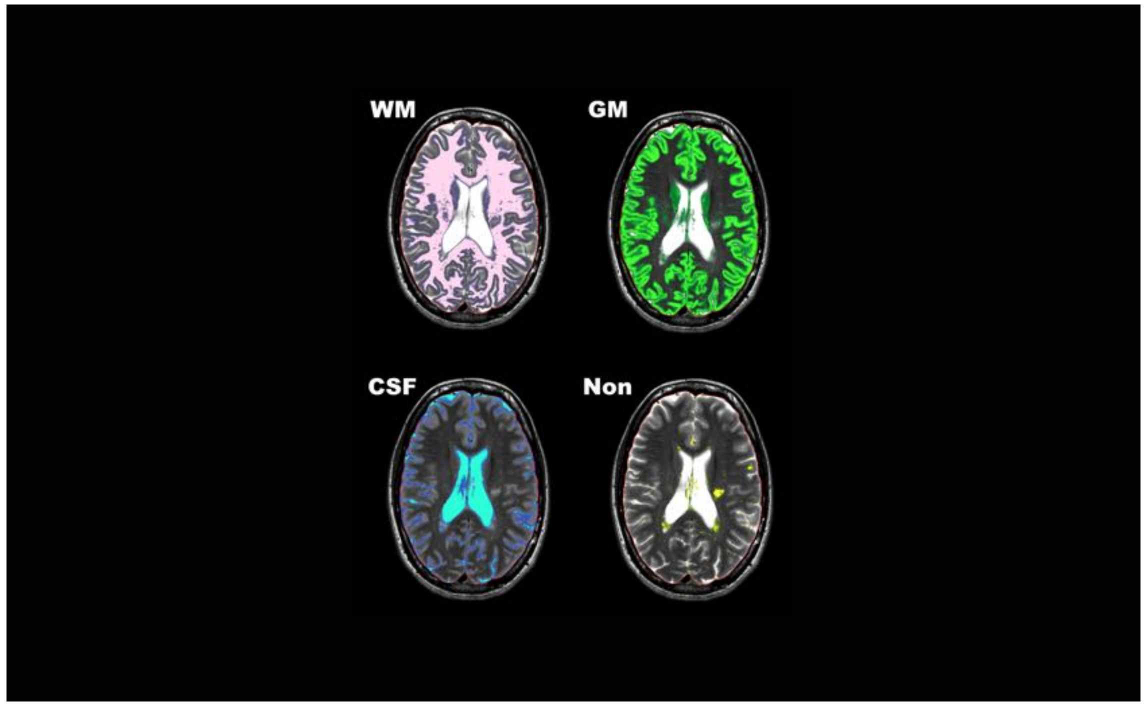


Fig. 4

Fig. 4. Synthetic tissue mapping, which converts the T1, T2 and PD SyMaps into white matter (upper left), grey matter (upper right), CSF (bottom left) and the remaining Non-WM/GM/CSF tissue (NON) maps (bottom right).

# Quantification – objective decision support

SyMRI brings the clinician flexible imaging and quantitative tissue assessment for neurodegenerative diseases, all based on one single MRI scan. Using synthetic MRI, the software enables automated tissue characterization and volume estimation of brain tissue, providing objective decision support.

Intuitive tools are included to easily mark out and measure, for example, Multiple Sclerosis (MS) lesion load, tumor volume, or ventricle volume. With SyMRI, patient follow-up for neurodegenerative diseases can be based on quantitative measurements.

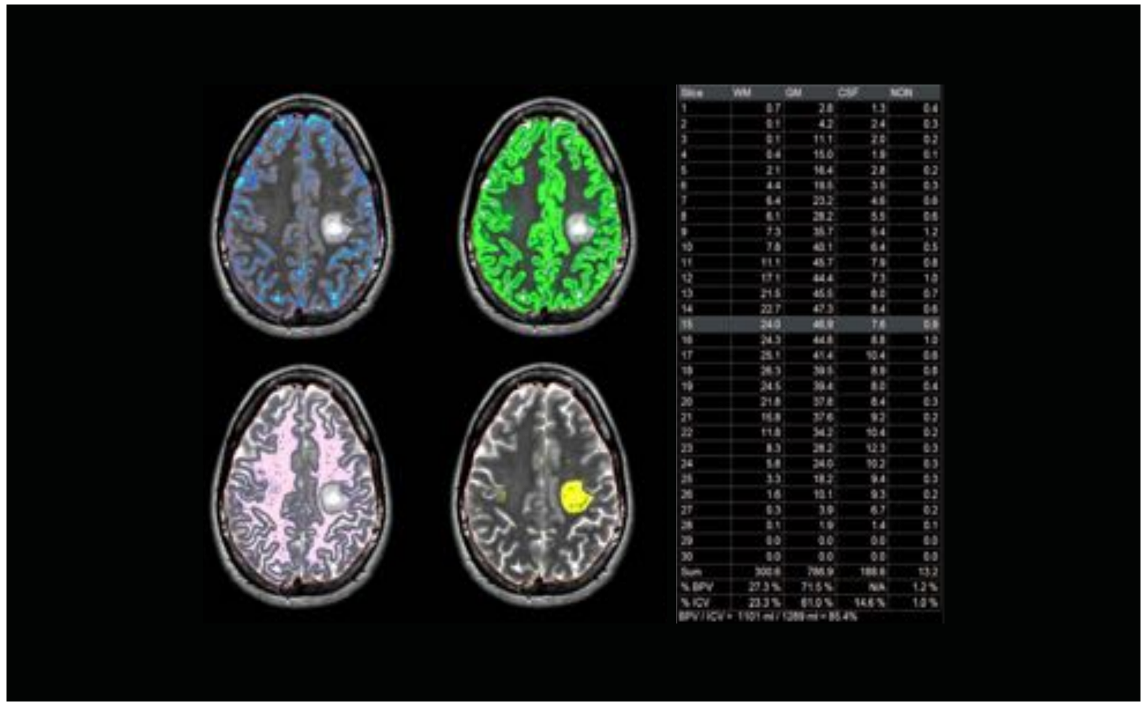

Fig. 5

Fig. 5. Synthetic tissue mapping. SyMRI automatically finds the intracranial volume (red line) and produces partial volume maps for cerebrospinal fluid (blue), grey matter (green), white matter (pink) and remaining tissue (yellow). Volumetric data is automatically presented in a table.

## Characterization and measurement of brain tissue

SyMRI automatically characterizes and measures cerebrospinal fluid (CSF), white matter (WM), gray matter (GM), and remaining tissue. The intracranial cavity and the tissue maps are segmented in a few seconds. Volumetric information is provided for the complete intracranial volume (ICV), per slice and per region of interest.



## Automatic measurement of brain atrophy

The Brain Parenchymal fraction (BPF) is a ratio that is calculated based on automatic identification of ICV, brain tissue and CSF. BPF is a valuable and clinically used measurement for brain atrophy in patients with neurodegenerative diseases such as MS and dementia.

## Quantitative measurements of myelin

Precise in vivo myelin measurements are valuable for differential diagnostics of white matter changes, and to study treatment response in demyelinating and neurodegenerative disorders.

Myelin plays an important role in the development of the nervous system where it insulates nerve fibers and greatly enhances the signal transmission speed. Demyelination caused by disease or aging impairs signal transmission and may lead to atrophy and brain dysfunction.

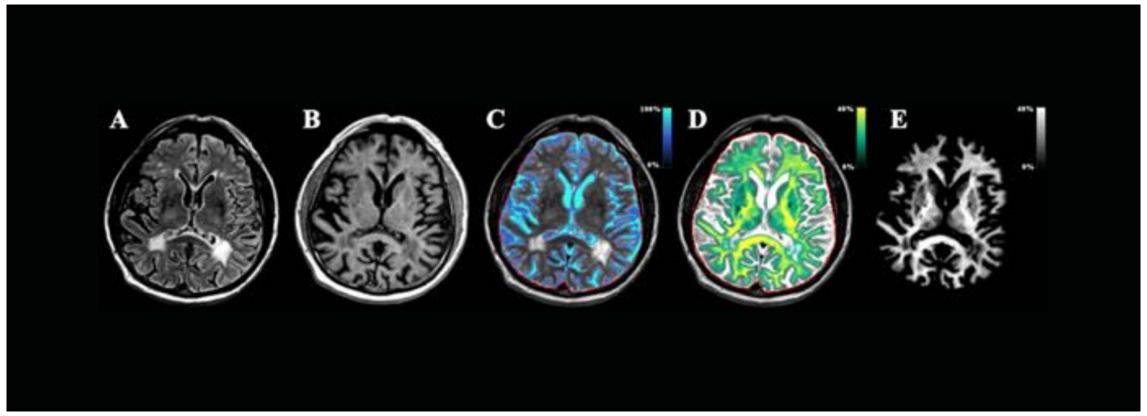


Fig. 6

Example of myelin mapping in a patient diagnosed with HDLS. Based on the quantification maps conventional images such as FLAIR (A) and T1W (B) can be synthesized for visual aid. At first, the intracranial volume (red line) and CSF (blue) are segmented to segment the brain (C).

Then, the brain is decomposed into the partial tissue volumes, including myelin (D). Summation of all myelin partial volume voxels provides the total myelin volume in the brain (E). This patient (58 years old male) had a myelin volume of 153 mL, a brain volume of 1069 mL (myelin ratio 14.3%) and an ICV of 1409 mL (myelin ratio 10.9%). The brain to intracranial volume ratio (BPF) was 75.9%.

Patented and marketed under the trade name REMyDITM (Rapid Estimation of Myelin for Diagnostic Imaging) SyMRI software generate parametric PD, R1 and R2 SyMaps and measure the presence of myelin by its effect on the properties of the surrounding cellular water in a highly reproducible fashion.

### User defined segmentation

SyMRI includes a User Mask for measuring tissue volume in a region of interest (ROI) defined by the user. This can be used to measure MS lesion load, tumor volume, entricle volume or other volumes for improved diagnostic capability.

### SyMaps – Parametric maps

The quantified maps provide the absolute values of physical properties of your patient, comparable with the Hounsfield units in CT imaging. This is unlike the arbitrary scale of conventional imaging. Healthy tissue has a certain band of normal values, which may deviate in case of pathology. Apart from enabling advanced clinical research, we believe that SyMaps will gain diagnostic importance in the future, since the absolute scale permits direct comparison between patients.

SyMaps can be saved and exported as DICOM file(s) for later analysis in third party applications or research tools such as MatLab.

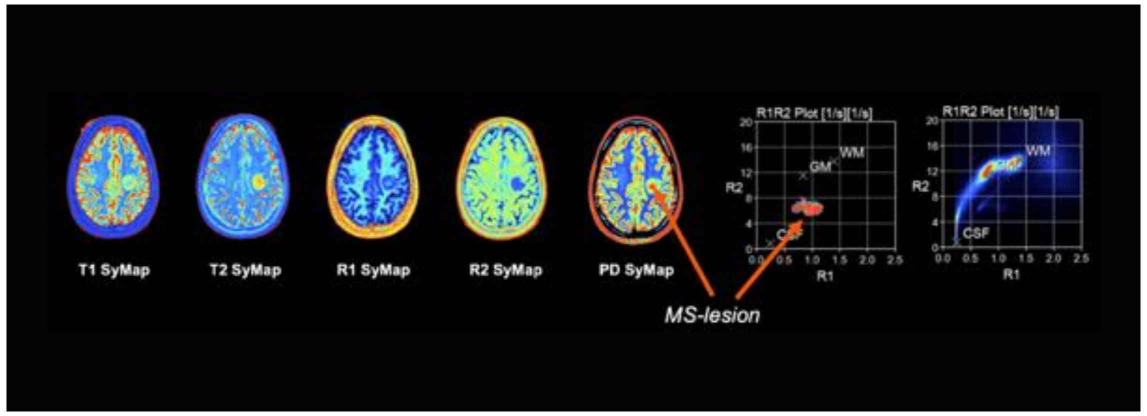


Fig. 7

Fig. 7. Parametric SyMaps and R1R2 plots. Frpm left to right: T1 SyMap, T2 SyMap, R1 SyMap, R2 SyMap, PD SyMap, R1R2 plot of MS-lesion, global R1R2 plot.



## Key value points

SyMRI uses a fundamentally different approach to MRI as it measures tissue properties and synthesizes images based on absolute measurement of these properties rather than generating a fixed contrast image. Thus, SyMRI can produce adjustable contrast images and quantitative data from a single 5-6 minutes scan.

The single pulse sequence acquisition can also generate a range of different image contrasts, allowing short examination time and high patient throughput.
The contrast settings are adjustable after the images have been acquired for optimal image quality and flexibility.

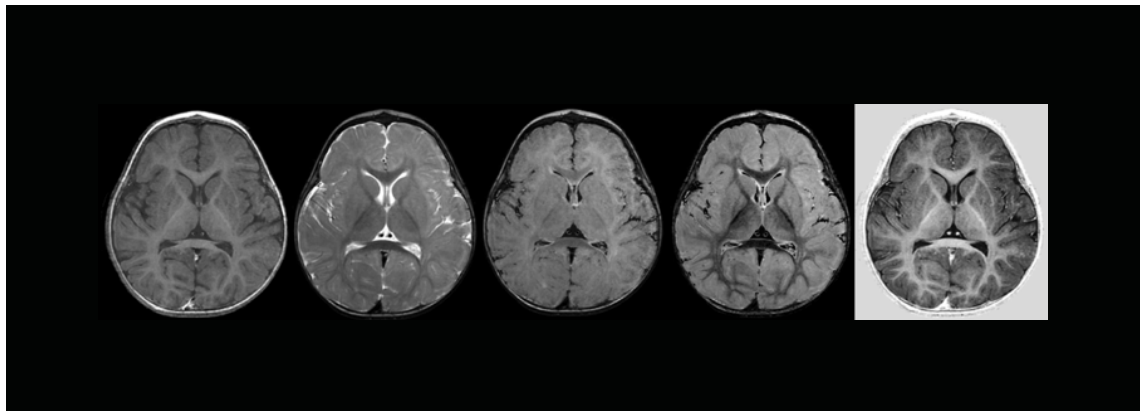

Fig. 8

Fig. 8. Examples of SyMRI contrast images from a pediatric patient. From left to right: T1-weighted, T2-weighted, T2W FLAIR, DIR, PSIR.

## One quick scan

A traditional neurological MRI-scan takes approximately 30 min per patient. Images are acquired sequentially and each image type requires a separate pulse sequence with specific scanner settings. Because of this, other imaging modalities are often used even when MRI would be clinically preferred. There is therefore a need for increased efficiency to make MRI available for a broader patient base.

With SyMRI, a single scan generates T1-weighted, T2-weighted, FLAIR, and Inversion Recovery images in as little as one-third the total time it would take to acquire each contrast separately. The time saved could allow clinicians to scan more patients per day and improve patient experience.

Short scan times also make it possible to use MRI as a screening technique for neurological diseases. A fast scan can be used to exclude a pathology or for quick patient follow-up. A full examination can then be completed if something is found on the first scan, thus limiting unnecessary examinations.

## Adjustable contrasts

MRI images are traditionally examined manually in order to make sure adequate images have been obtained. If the contrast settings were not optimal, the patient may have to be recalled for another scanning session.

With SyMRI, once the examination is completed, the contrast can be adjusted by manipulating repetition time TR, echo time TE and inversion delay time TI. Quantitative images can be synthesized at any combination of TR, TE and TI values, for maximum flexibility. Adjustable contrasts help to ensure that no details are missed, and allow clinicians to optimize image quality. The possibility of recreating any T1-weighted, T2-weighted, FLAIR or Inversion Recovery image after the patient has left also helps ensure that no contrasts are missed without re-scanning the patient.

A prospective study on 109 subjects, read by 7 neuroradiologists, described a comparison of conventionally acquired T1W, T2W, PDW, T1-FLAIR, T2-FLAIR and STIR images with their synthetic counterparts, which were all based on the same sequence, acquired in about one-third of the time. Diagnostic quality, morphologic legibility, radiologic findings indicative of diagnose and artifacts were judged similar for both methods (Tanenbaum et al, AJNR 2017:38; 1103-1110). A comprehensive overview of the potential of synthetic MR imaging is provided by Hagiwara et al . Invest Radiol. 2017 Mar 3.



# Example on the pediatric application of SyMRI® IMAGE

Dr. Blaise Jones and Dr. Jim Leach, Cincinnati Children's Hospital Medical Center. Synthetic MRI has been evaluated on pediatric patients since summer 2014.

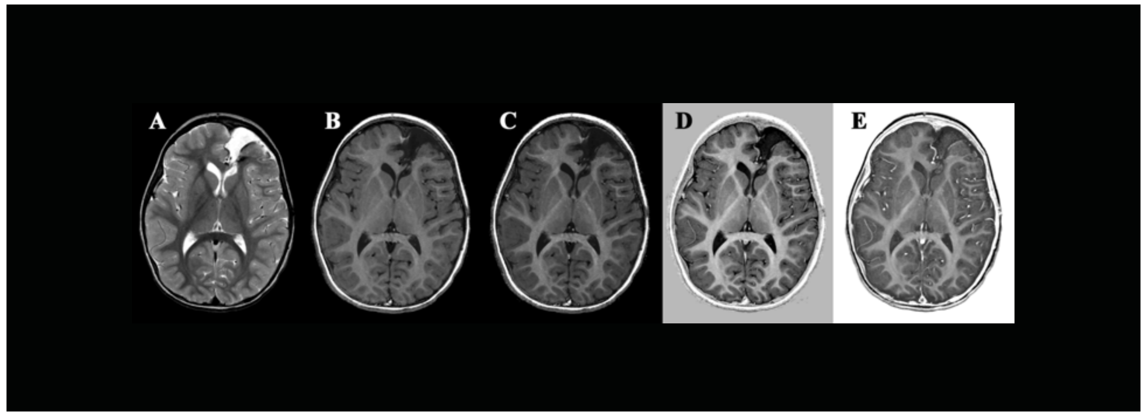


Fig. 9

Fig. 9. Various synthetic contrasts on an 11-month old patient. Besides the 'normal' T2W (A) and T1W (B) images, other contrasts can be helpful, such as an extremely T1W (TR = 100 ms, (C)) or a Phase-Sensitive IR image (TI = 500 ms for GM/WM contrast (D) and TI = 10 ms to highlight vessels (E)).

At CCHMC synthetic imaging has been evaluated on a small group of pediatric cases, initially in two steps. At first it was ensured that the synthetic images diagnostically were sufficient in comparison with conventional sequences. The true strength of synthetic imaging, however, is the possibility of tuning image contrast afterwards and generating contrasts that usually are not acquired. Therefore the use of synthetic imaging, including interactive contrast changes during review, is now ongoing as the second step of evaluation. In the figure examples are displayed of settings that may be used for pediatric cases.

We anticipate that synthetic imaging is going to help us discern subtle differences at grey matter to white matter interfaces, for example in epilepsy cases. Furthermore we expect that the quantitative T1, T2 and PD maps can assist us in monitoring the myelination process of white matter during the first years of brain development.

# Example on MS application of SyMRI® NEURO

Dr. Anders Swenningsson and Dr. Richard Brigander, Umeå University Hospital, Umeå, Sweden.
Synthetic MRI has been evaluated on MS patients since 2009.

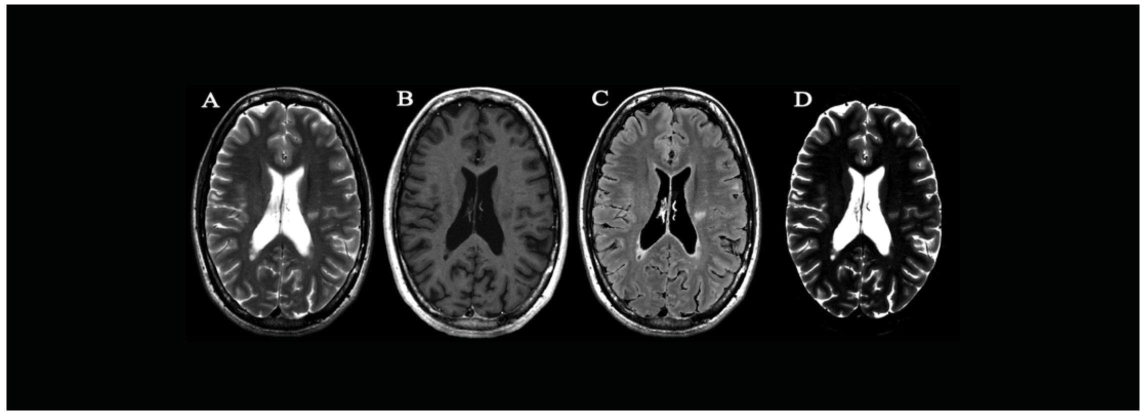


Fig. 10 Fig. 10. Synthetic images of an MS patient post-Gd, T2W (A), T1W (B), FLAIR (C) and STIR (D).

Synthetic imaging has been used at Umeå University Hospital for many years with over 1500 cases now acquired. SyMRI NEURO is used as a quantification tool to calculate the Brain Parenchymal fraction (BPF) and monitor brain atrophy in MS patients. BPF values are also stored in the national MS registry.

Currently, synthetic imaging is used as a fast and efficient single pulse sequence acquisition for follow-up examination once an MS diagnosis has been made. The rapid throughput of the SyMRI sequence allows regular check-ups of our patients to monitor response to treatment, without the need for a lengthy and expensive full brain examination.



# Example on the Sturge-Weber syndrome of SyMRI® REMyDI

Dr. Christina Andica and Dr. Akifumi Hagiwara, Juntendo University School of Medicine, Tokyo, Japan.

Sturge-Weber syndrome (SWS) is a developmental disorder with leptomeningeal angiomatosis as the major pathological abnormality. Typically, a prominent hypo-intensity on T2W images is observed in the white matter underlying the angiomatosis in an infant with SWS. In this example a 4 month-old male infant was referred to our hospital with a few episodes of left leg twitching. Clinical examination showed a right facial angiomatosis and a left leg hemiparesis. SyMRI was acquired on a 3T Discovery 750 system (GE Healthcare).

To be able to view a high image contrast for pediatric brains with higher water content, more extreme settings for the synthetic images were chosen than typical for conventional images. For example, for T2W we used TE/TR = 150/15000 ms, for T1W a TE/TR = 10/100 ms and for the Double IR a TE/TR = 10/6000 ms. Since all images are derived from the same sequence there is no scan time penalty to do so (see Figure 1).

The synthetic DIR clearly demonstrated myelinated white matter. Accelerated myelination was confirmed by the myelin map, where a substantial left-right difference was observed (Figure 1D). The myelin volume in the right hemisphere was 7.9 ml, in comparison to the myelin volume in the left hemisphere of 4.2 ml. The use of SyMRI facilitates the diagnosis of SWS because it both provides high-contrast images and objective measurements. Quantitative detection and follow-up may improve the prognosis by preventive anti-epileptic treatment.

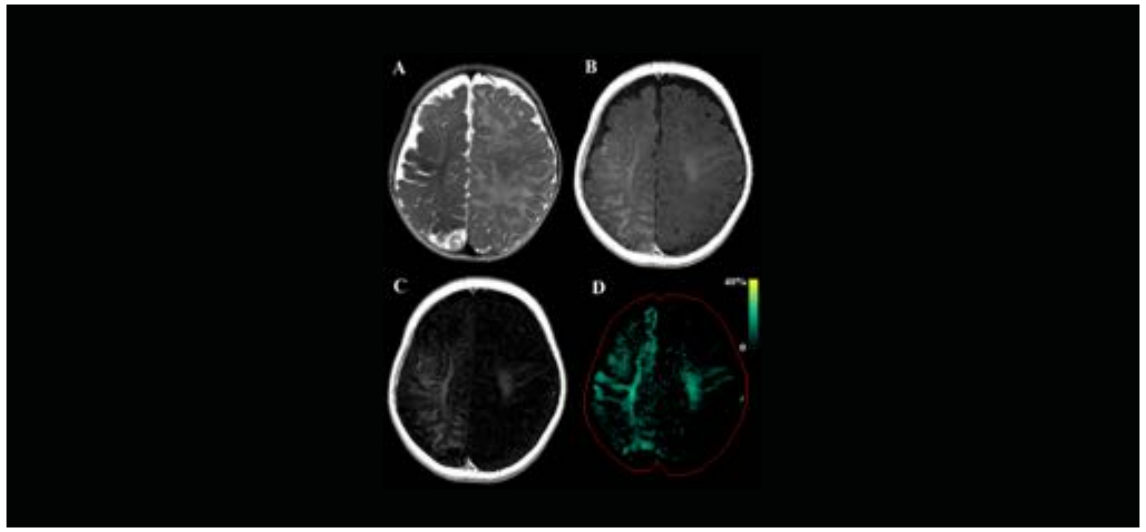


Fig. 11 Representative slice for a 4 month-old patient with Sturge-Weber syndrome. In order to enhance image contrast, extreme settings for the synthetic images were chosen. A) T2W (TE/TR = 150/15000 ms), B) T1W (TE/TR = 10/100 ms) and C) Double IR (TE/TR = 10/6000 ms with TI1 = 860 ms and TI2 = 3490 ms). The myelin map (D) shows the hypermyelination in the right hemisphere.

# Example on malignant glioma

Case from a Swedish university hospital where synthetic MRI has been evaluated on tumor patients.

## Background

Initial CT-scan indicates a tumor in the left frontotemporal region and the following scan with intravenous contrast confirms the finding (fig 12).

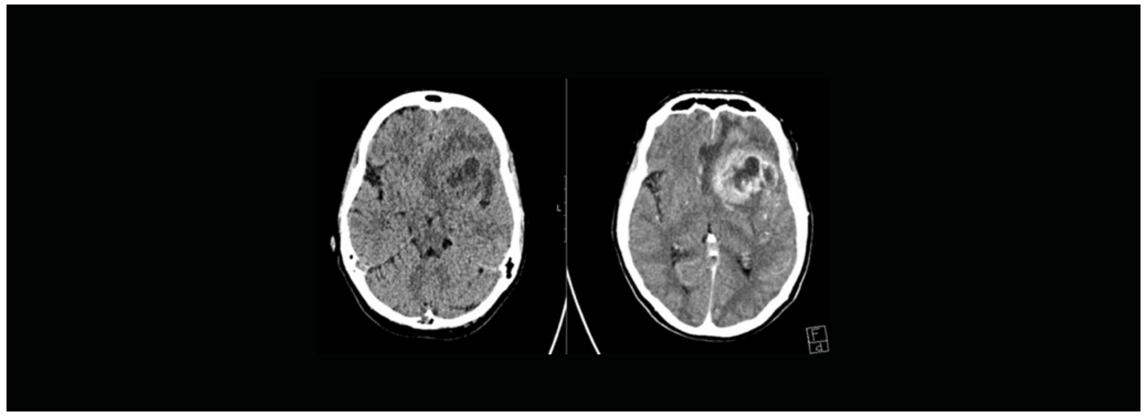

Fig. 12 CT images of the patient at first visit, left pre-contrast, right post-contrast

## Imaging set-up

Two days later a MR-exam is performed to evaluate the tumor and its relation to the surrounding brain. In addition to the conventional images, SyMRI images before and after contrast agent administration were performed. Images show a large, heterogeneous tumor with partial necrosis, contrast enhancement and a moderate peritumoral edema. The suggested diagnosis is malignant glioma. The tumor is closely related to the left middle cerebral artery and also to structures in the brain related to speech function. The mass effect causes a midline shift and an incipient uncal herniation on the left side, but no hydrocephalus.

The advantage for using SyMRI in these cases is that it provides the synthesized images and, using the same scan time, also generates quantitative measurements, such as the R1 and R2 relaxation maps (the inverse of T1 and T2 relaxation times). These are not yet part of normal clinical evaluation, but pathology analysis or segmentation based on these maps could be of help in the future e.g. regarding a more objective tumor delineation and tumor volumetrics.



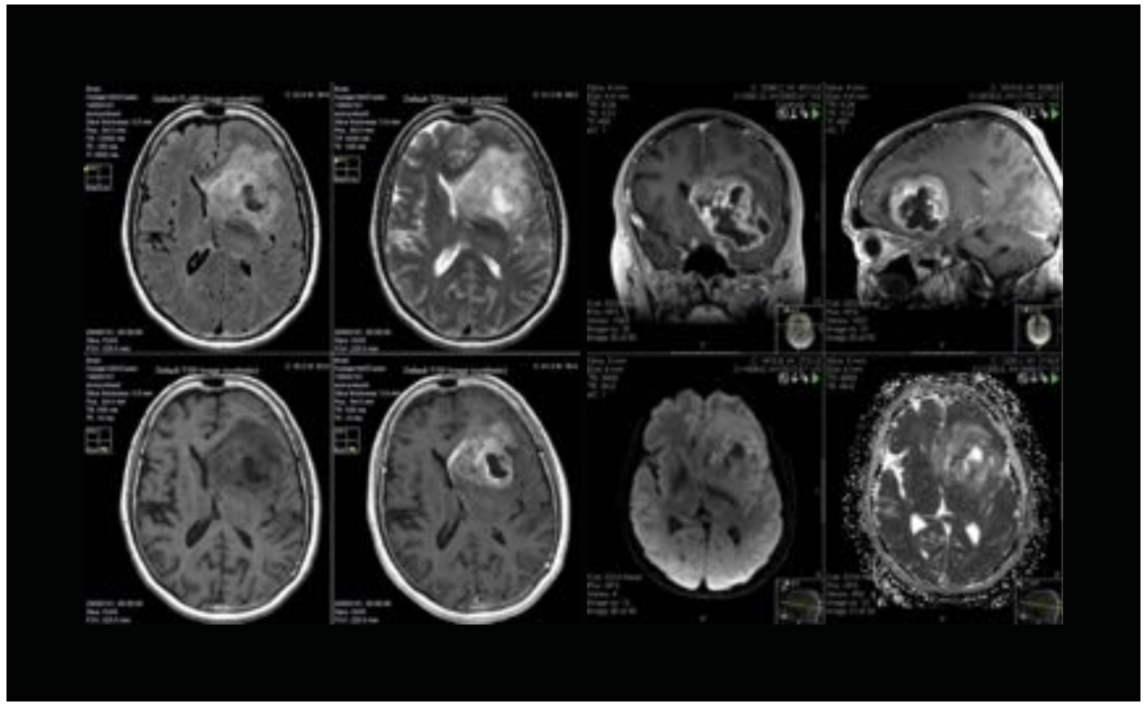

Fig. 12 Set-up for the MR examination. On the left panel the axial SyMRI images: FLAIR (TR/TE/TI = 12000/100/2600 ms), T2W (TR/TE = 4500/100 ms), T1W (TR/TE = 500/10 ms) and T1W post-GD (TR/TE = 500/10 ms). On the right panel the conventional images; a coronal and sagittal reformat of a T1W BRAVO, diffusion-weighted (b=1000) and ADC map.

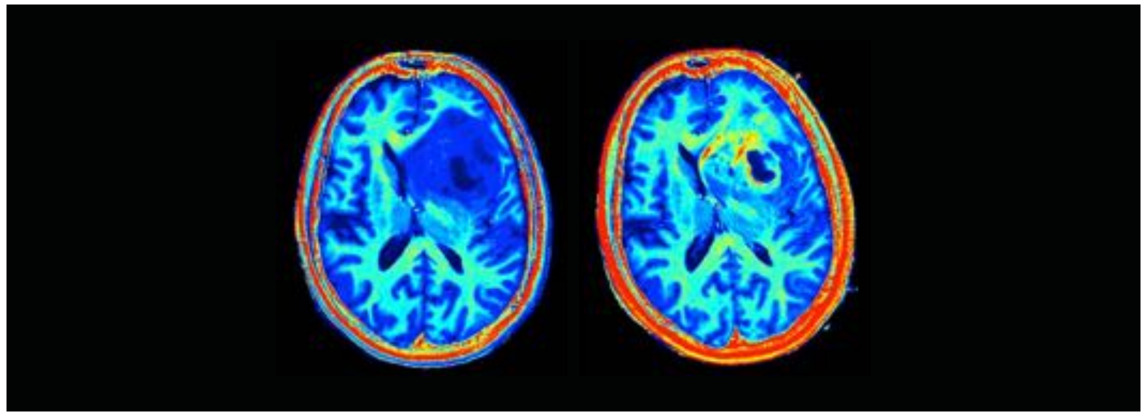

Fig. 13 Fig. 13. R1 map on a scale 0-2.5 s-1, left pre-GD, right post-GD. The T1W enhancing areas show values up to 3 s-1 after GD contrast, more than 3 times higher than the native R1 values.

# References

Details of the Synthetic MR MDME sequence are further described by Warntjes et al. Rapid magnetic resonance quantification on the brain: Optimization for clinical usage. Magnetic Resonance Imaging 60; 320-329 (2008).

The concept of synthetic MRI is described by Bobman et al. AJNR 6:265-269 (1985) and the signal equations for synthetic MR images are described by Maera and Barker. Evolution of the longitudinal magnetization for pulse sequences using a fast spin-echo readout: application to fluid-attenuated inversion-recovery and double inversion-recovery sequences. Magnetic Resonance in Medicine 54:241–245 (2005).

The prospective comparison of synthetic and conventional MR imaging was made by Tanenbaum et al, Synthetic MRI for Clinical Neuroimaging: Results of the Magnetic Resonance Image Compilation (MAGiC) Prospective, Multicenter, Multireader Trial. AJNR Am J Neurorad 38;1103-1110 (2017)

A comprehensive overview of the potential of synthetic MR imaging is provided in Hagiwara et al. SyMRI of the Brain: Rapid Quantification of Relaxation Rates and Proton Density, With Synthetic MRI, Automatic Brain Segmentation, and Myelin Measurement. Invest Radiol. 2017 Mar 3



SyMRI is a CE-marked, US FDA 510(k) cleared product.

SyntheticMR

syntheticmr.com
info@syntheticmr.com
+46 (0) 13 101 650