Synthesized Magnetic Resonance Imaging and SyMRI®

Theory and Application

A white paper

Marcel Warntjes, PhD

SyntheticMR

Table of contents

SyMRI® Technical Overview

Synthetic MR Imaging

Synthesized MR image acquisition and reconstruction is a new concept with great potential to reduce exam time, improve patient experience, and bring novel diagnostic functionality and visual insight to the reader.

Synthetic imaging is based on absolute quantification of physical parameters that govern the image MRI signal intensity - namely T1 relaxation, T2 relaxation, and Proton Density (PD).

These physical properties are used in combination with virtual scanner settings for echo time TE, repetition time TR and inversion delay time TI, to synthesize conventional images such as T1W, T2W, FLAIR, STIR, phase-sensitive inversion recovery or double inversion recovery images. In other words, a whole range of conventional images can be reconstructed using a single quantification scan.

SyMRI pulse sequence

The proprietary SyMRI pulse sequence from SyntheticMR is a 2DFSE multi-dynamic, multi-echo (MDME) sequence, which is performed using an interleaved slice-selective 120 degrees saturation and multi-echo acquisition. While the saturation acts on a slice n, 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, while the acquisition of signal is near-continuous.

There are four different options – or dynamics – of n and m performed, resulting in four different delay times (TI), which is automatically done without user interaction. Because the number of echoes of the acquisition is fixed to two, at two different echo times, the result of each MDME acquisition is eight (complex) images per slice (4 saturation delays, at 2 echo times, Figure 1). More details on the sequence can be found in Warntjes et al. 2008 (1).

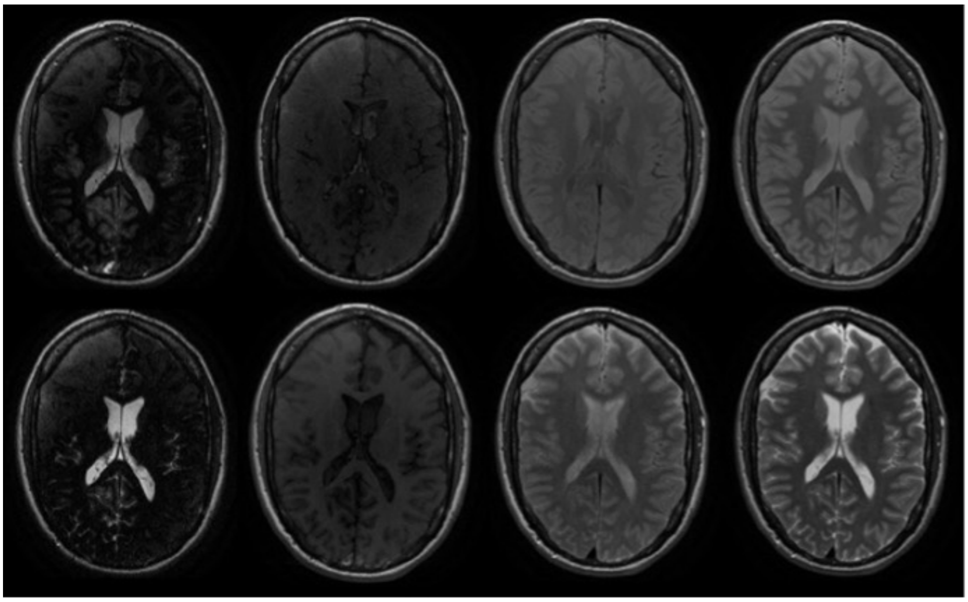


Fig. 1. Raw MDME images of a single slice. The images are complex and hence have a real and imaginary component. Only the modulus (sqrt(sqr(real) + sqr(imaginary))) is shown here.

SyMRI post-processing

The MDME images all exhibit different effects of the T1 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 eight images per slice and calculates the T1 and T2 relaxation values. Additionally, it calculates the proton density and the amplitude of the B1 field according to the below algorithm:

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

Where A is an overall intensity scaling factor taking into account the coil sensitivity, the RF chain amplification and the voxel volume, α is the applied 90 degrees excitation flip angle and "θ" is the applied 120-degrees saturation pulse angle. Figure 2 shows an example of T1, T2, PD, and B1 SyMaps®. It is also possible to show the relation rates, specifically R1 (1/T1) and R2 (1/T2). The processing time is approximately 8 seconds.

In SyMRI processing, B1 is not shown to the user, as it has no clinical relevance.

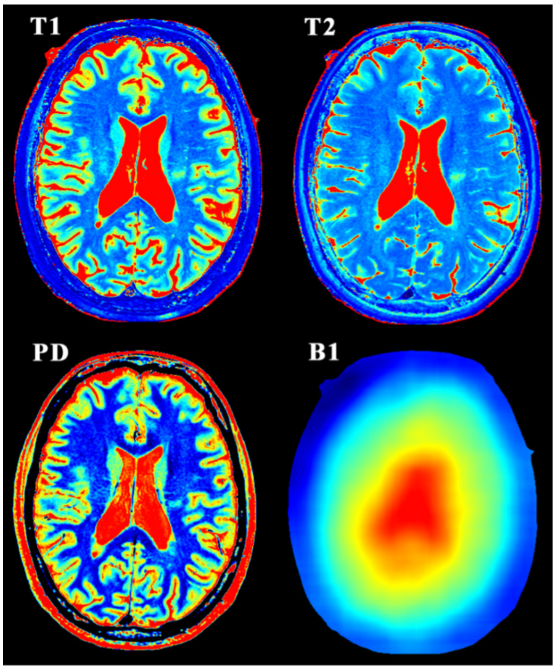


Fig. 2. Processed MDME images, resulting in SyMaps of T1 and T2 relaxation time, proton density, and the B1 field.

SyMaps® Parametric maps

The quantitative SyMaps provide absolute values of the physical properties of the patient, comparable with the Hounsfield units in CT imaging and unlike the arbitrary scale of conventional imaging. Healthy tissue has a certain band of normal values, which may deviate in the presence of pathology. The parametric SyMaps therefore enables assessment and tracking of underlying tissue changes in, for example, peritumoral edemas, tumor perfusion or lesions. The absolute scale permits robust direct comparisons over time or between patients.

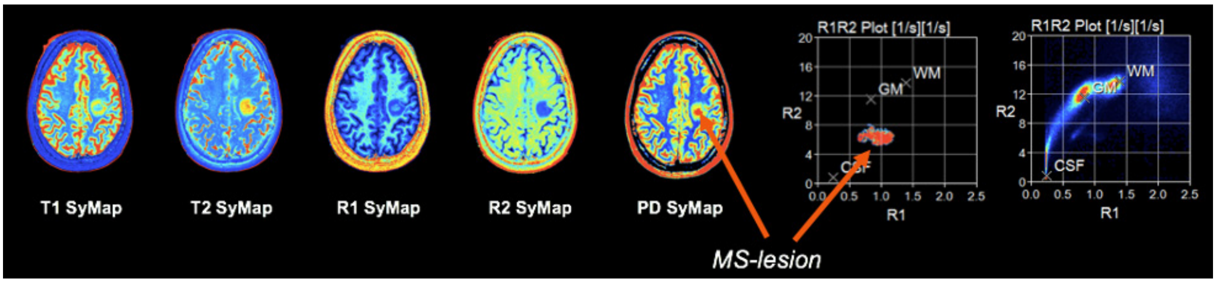


Fig. 3. Parametric SyMaps(R) and R1R2 plots. From left to right: T1 SyMap, T2 SyMap, R1 SyMap, R2 SyMap, PD SyMap, R1R2 plot of MS-lesion, global R1R2 plot.

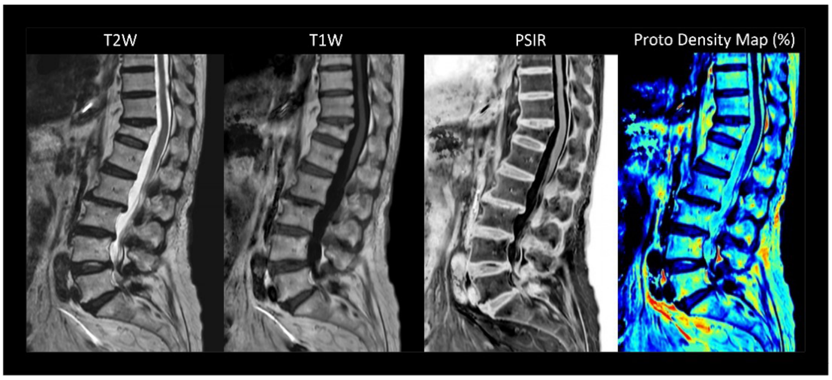


Fig. 4. Example of synthetic images of the spine of an 86-year-old female patient with an old fracture at 3T. Displayed are the synthetic T2W (TE/TR = 100/4500 ms), T1W (TE/TR = 10/650 ms) and a PSIR (TE/TR/TI = 25/15000/10 ms). On the far right the Proton Density map is shown on a scale 50-150%. Proton density is believed to be inversely proportional to bone density.

Creation of synthetic images

Once T1, T2 and PD values are known, SyMRI can generate synthetic contrast-weighted images 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 α is set to 90 degrees.

$$\mathrm{S} = \mathrm{PD} \cdot \exp(-\mathrm{TE}/\mathrm{T}_2) \cdot (1 - \exp\,(-\mathrm{TR}/\mathrm{T}_1)) \qquad \textbf{(Eq.2)}$$

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

$$\mathrm{S} = \mathrm{PD} \cdot \exp(-\mathrm{TE}/\mathrm{T}_2) \cdot (1 - 2 \cdot \exp(-\mathrm{TI}/\mathrm{T}_1) + \exp(-\mathrm{TR}/\mathrm{T}_1)) \qquad \textbf{(Eq.3)}$$

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.

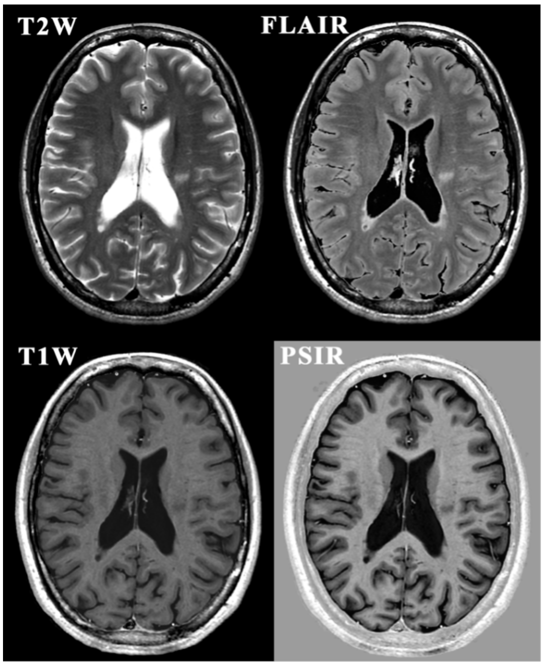


Fig. 5. Examples of SyMRI images, based on the T1, T2, and PD maps of Fig. 2 including FSE images such as T1W and T2W as well as IR-FSE images such as FLAIR and PSIR.

The contrast-weighted images generated in SyMRI have been shown to be of diagnostic quality and can be generated in the third of a time compared to conventional scans (2).

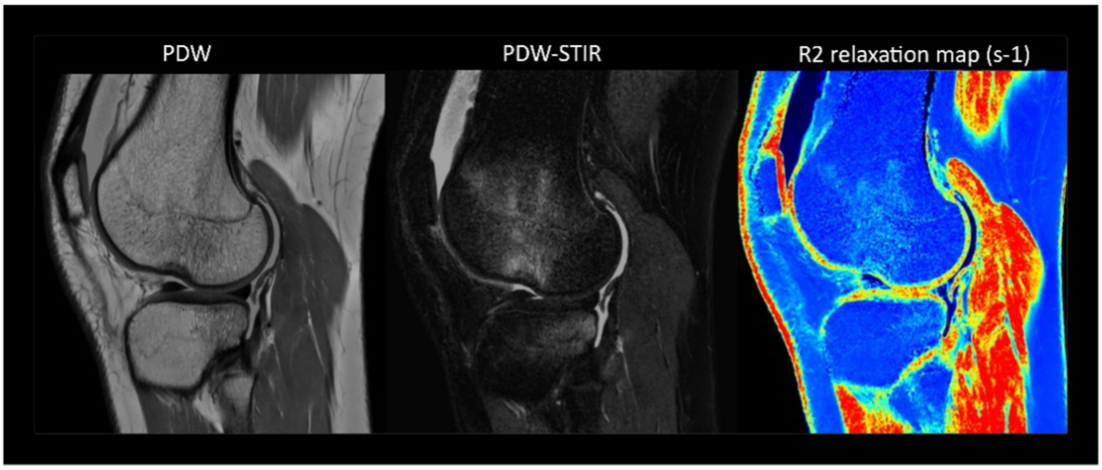


Fig.6. Synthetic images of a knee with a cruciate ligament tear, cartilage damage and distinct bone edema: PDW (TE/TR = 10/8000 ms) and PDW-STIR (TE/TR/TI = 10/15000/290 ms). On the right there is R2 relaxation rate map. The R2 relaxation rate is the inverse of the T2 relaxation time and can be used to characterize the cartilage damage.

Brain Tissue Segmentation

The T1, T2 and PD SyMaps can also be used to generate tissue segmentation maps, in addition to the synthesized contrast-weighted images. SyMRI automatically generates segmentation maps of white matter, gray matter, cerebrospinal fluid and myelin in the brain.

The tissue 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.

SyMRI also finds the intracranial outline and calculate brain volumes such as intracranial volume (ICV) and brain parenchymal volume (BPV). SyMRI automatically calculates the brain parenchymal fraction (BPF), a ratio of ICV and CSF, and a valuable biomarker to measure and track brain development and atrophy.

Validation of the technique can be found in for example Ambarki et al. 2012 (3) and Vågberg et al. 2015 (4).

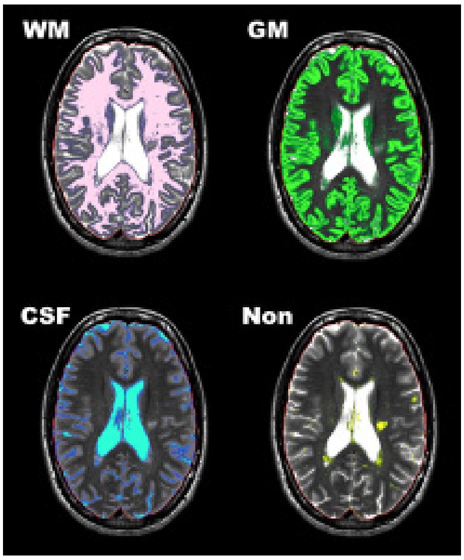


Fig. 7. Synthetic tissue mapping, which converts the T1, T2 and PD SyMaps® into white matter (upper left), grey matter (upper right), CSF (bottom left) and the remaining non-WM/GM/CSF tissue (NON) maps (bottom right).

Myelin correlated volumes

SyMRI measures the presence of myelin by its effect on the surrounding cellular water properties in a highly reproducible fashion.

The myelin model divides each voxel of the MR image into four compartments. The four partial volume compartments are myelin partial volume (VMY); cellular partial volume (VCL); free water partial volume (VFW); and excess parenchymal water partial volume (VEPW). The content of each partial volume compartment can range from 0 to 100%, with the sum of the four compartments always adding up to 100%. Each partial volume compartment has its own relaxation properties and can be described by its R1, R2 and PD values.

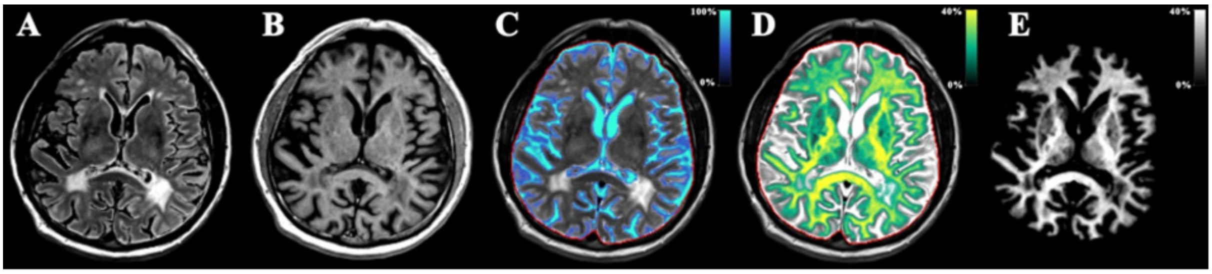


Fig. 8. Example of myelin mapping in a patient diagnosed with HDLS (Hereditary diffuse leukoencephalopathy with spheroids). Based on the quantification maps, conventional images such as FLAIR (A) and T1W (B) can be synthesized for visual aid. First, the intracranial volume (red line) and CSF (blue) are segmented to segment the brain (C). Then, the brain is broken down 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-year-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%.

The automatic myelin detection was histologically validated study by Warntjes et al. (2017) on 12 brain specimen stained with Luxol Fast Blue, a marker specific for myelin. The study found a good correlation between LFB and the myelin maps of r = 0.74. This supports the validity of the myelin measurement by using the MR imaging quantification method in SyMRI.

A study from Karolinska Institutet in Stockholm, Sweden, provided further validation in a study aimed to assess the specificity, robustness and clinical value of the myelin imaging technique in patients with multiple sclerosis. In the study three ex-vivo MS brain samples were included, as well as 71 MS patients and 21 healthy, age-matched controls. The study found good correlation between the myelin-related stains and the imaging results, and the myelin fractions also correlated with follow-up disability (5).

Reference curves

SyMRI automatically generates age-stratified reference curves that can be used to quickly estimate the patient against a healthy population. The reference curves can be used from age 0 to 99 years old. The reference curves are based on clinical and validated data (6) (7).

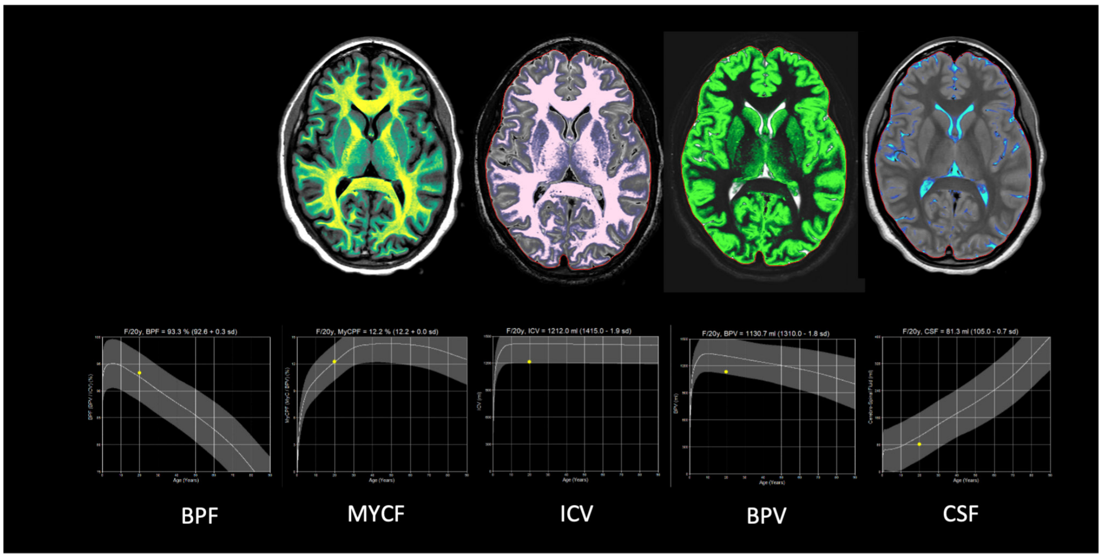


Figure 9: Tissue segmentation maps and reference curves of a healthy individual, where the yellow dot clearly indicates the patient compared to a healthy population.

Advantages of SyMRI

SyMRI measures tissue properties and creates synthetic contrast-weighted images and quantitative data from a single fast scan.

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

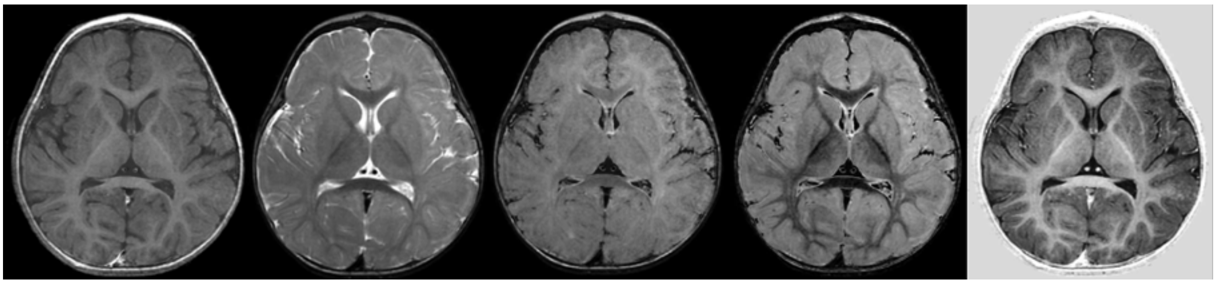


Fig. 10. Examples of SyMRI® contrast images from a pediatric patient. From left to right T1W, T2W, T2W FLAIR, DIR, PSIR.

Improved efficiency

With SyMRI, a single scan generates T1-weighted, T2-weighted, FLAIR, and Inversion Recovery (IR) images in as little as one-third the total time* (2). Time savings could allow clinicians improve throughput and patient experience.

Short scan times could also show value in a number of other applications, including making MRI a valuable screening tool for neurological disease, excluding a specific pathology, or for fast and efficient patient follow-up.

The synthetic contrast-weighted images can also be adjusted for any combination of TR, TE and TI. This enables the clinician to manually generate additional contrast weightings and optimize the scanner settings even after the patient has left, reducing the risk of recall.

Within MSK this is particularly useful as the settings can be manually adjusted to highlight tissue depending on the clinical question, helping to ensure that no detail is missed.

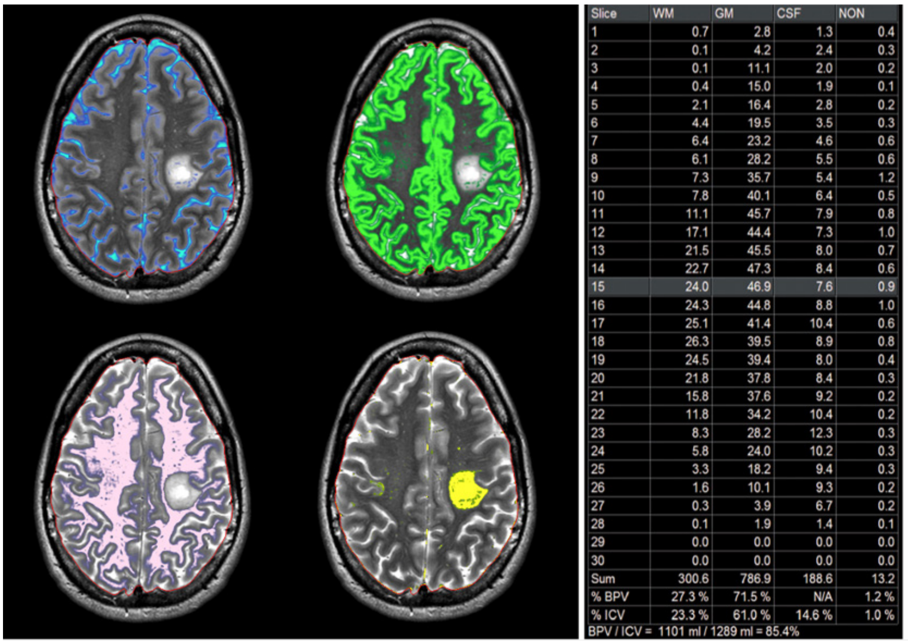
More precise diagnosis and monitoring

The automatically generated tissue segmentation maps and volumes provide clinicians with objective decision support. The ability to compare the patient to a healthy reference population provides further support in the diagnosis and monitoring of patients.

Because SyMRI utilizes the absolute tissue properties of the patient to generate the tissue maps and volume measurements, they are virtually independent of the scanner settings and even the scanner make or model. SyMRI produces robust and reproducible results that are comparable across time, as well as between scanners (8). This enables patients to be scanned at any scanner at follow-up scans and can help simplify the booking process.

The tissue measurements have been optimized for very young children and can be used for patients as young as neonates (9).

* When considering total time of each contrast separately.



Slice	WM	GM	CSF	NON
1	0.7	2.8	1.3	0.4
2	0.1	4.2	2.4	0.3
3	0.1	11.1	2.0	0.2
4	0.4	15.0	1.9	0.1
5	2.1	16.4	2.8	0.2
6	4.4	19.5	3.5	0.3
7	6.4	23.2	4.6	0.6
8	6.1	28.2	5.5	0.6
9	7.3	35.7	5.4	1.2
10	7.8	40.1	6.4	0.5
11	11.1	45.7	7.9	0.8
12	17.1	44.4	7.3	1.0
13	21.5	45.5	8.0	0.7
14	22.7	47.3	8.4	0.6
15	24.0	46.9	7.6	0.9
16	24.3	44.8	8.8	1.0
17	25.1	41.4	10.4	0.6
18	26.3	39.5	8.9	0.8
19	24.5	39.4	8.0	0.4
20	21.8	37.8	8.4	0.3
21	15.8	37.6	9.2	0.2
22	11.8	34.2	10.4	0.2
23	8.3	28.2	12.3	0.3
24	5.8	24.0	10.2	0.3
25	3.3	18.2	9.4	0.3
26	1.6	10.1	9.3	0.2
27	0.3	3.9	6.7	0.2
28	0.1	1.9	1.4	0.1
29	0.0	0.0	0.0	0.0
30	0.0	0.0	0.0	0.0
Sum	300.6	786.9	188.6	13.2
% BPV	27.3 %	71.5 %	N/A	1.2 %
% ICV	23.3 %	61.0 %	14.6 %	1.0 %

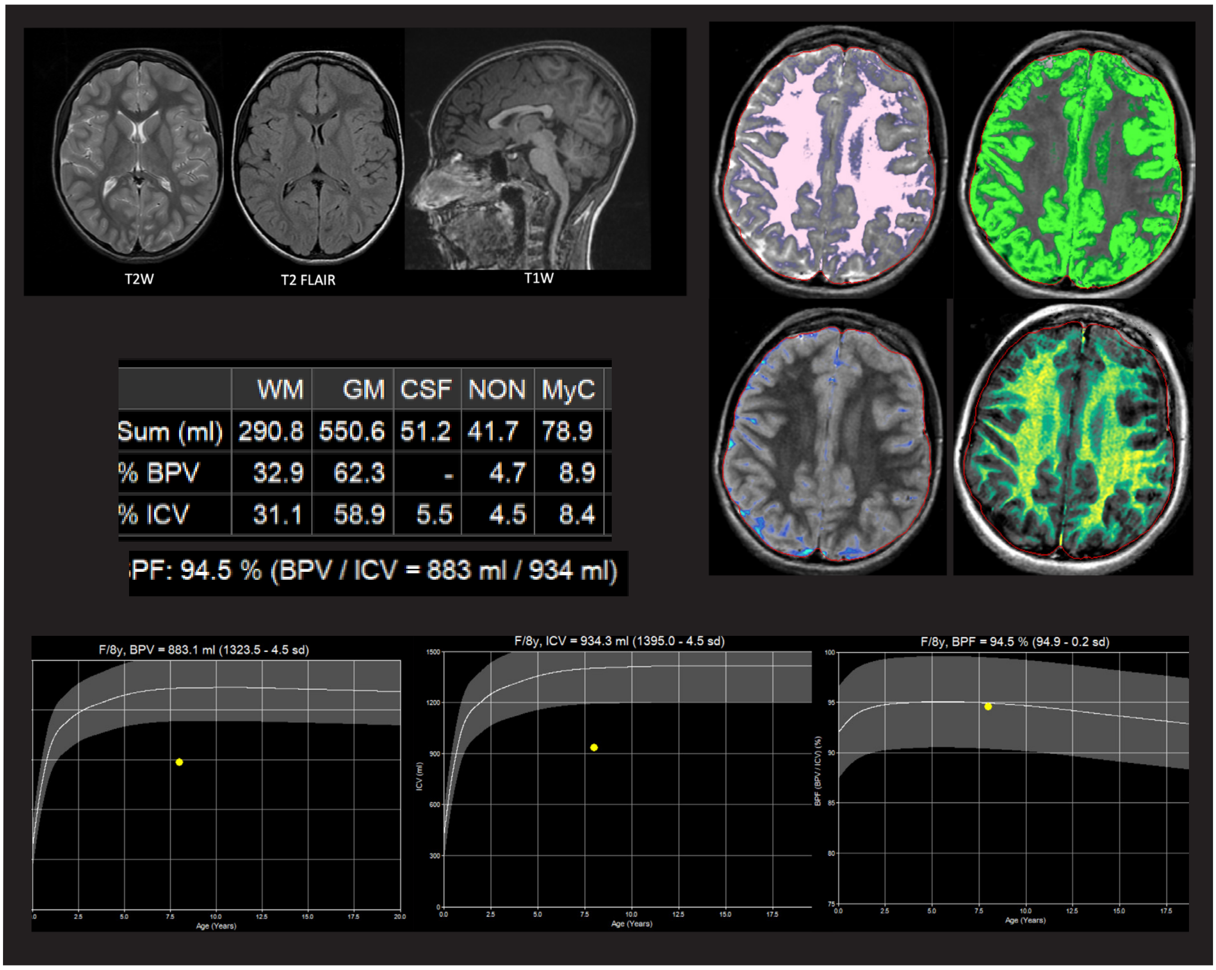
BPV / ICV = 1101 ml / 1289 ml = 85.4%

Fig. 11. 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.

Case study: Low cerebral volume

8-year-old female presenting with developmental delay.

The initial MR assessment of the brain revealed no abnormalities.



	WM	GM	CSF	NON	MyC
Sum (ml)	290.8	550.6	51.2	41.7	78.9
% BPV	32.9	62.3	-	4.7	8.9
% ICV	31.1	58.9	5.5	4.5	8.4

PF: 94.5 % (BPV / ICV = 883 ml / 934 ml)

Subsequent SyMRI sequence was performed, providing both scans and comparisons with normal patient population.

Scan shows ICV as very low for her age, as well as BPV. BPF (the percentage of intracranial volume taken up by the brain) was in the normal range, consistent with abnormal brain growth rather than volume loss.

As expected, both white matter and grey matter volume were decreased, as well as total myelin volume. Myelin fraction (percentage of BPV that is myelin) was in normal range, indicating that this is simply because of the small brain, rather than poor myelination. CSF volume is normal.

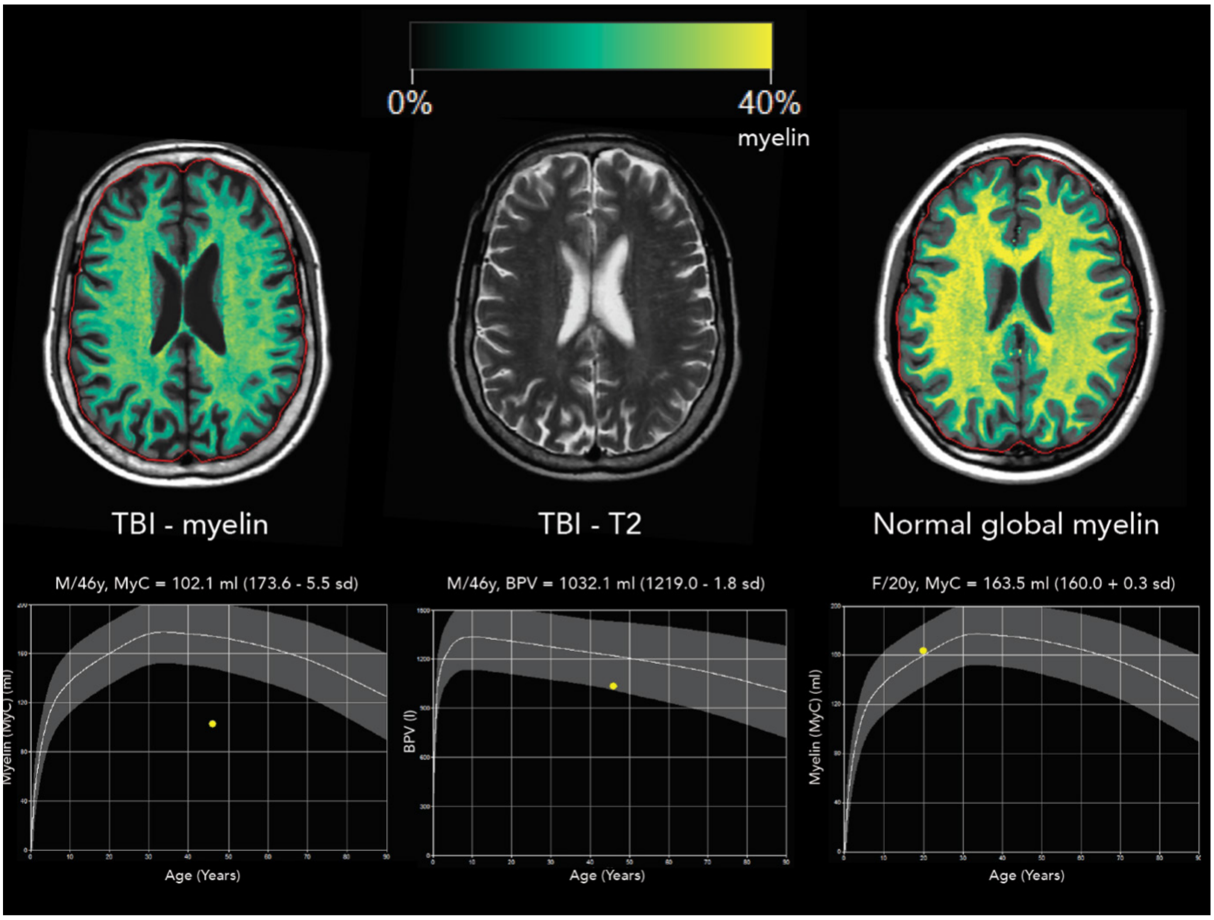
Overall findings are compatible with a primary abnormality of brain growth, suggesting a genetic cause.

Prognosis: Subsequent genetic testing revealed an AKT3 deletion, a known abnormality resulting in decreased brain growth and microcephaly.

Source: Dr. Leach, Cincinnati Children's Hospital

Case study: global myelin loss

46-year-old male with persistent headache following concussion.



There is global myelin loss in an otherwise normal-looking brain. When this appearance is compared to the normal global myelin example, it is apparent that the amount of yellow (representing highest myelin concentration) is substantially decreased. The reference curve shows that this patient's myelin content is 5 standard deviations below the mean, suggestive of severe impairment.

Source: Dr. Lefkowitz, SimonMed Imaging

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.

1) Warntjes et al. (2008), Rapid Magnetic Resonance Quantification on the Brain: Optimization for Clinical Usage, Magn Reson Med 2008:60;320-329

2) Tanenbaum et al. (2017), Synthetic MRI for Clinical Neuroimaging: Results of the Magnetic Resonance Image Compilation (MAGiC) Prospective, Multicenter, Multireader Trial, Am J Neuroradiol 2017; 10.3174/ajnr.A5227

3) Ambarki et al. (2012), Evaluation of Automatic Measurement of the Intracranial Volume Based on Quantitative MR Imaging, Am J Neuroradiol 2012; 10.3174/ajnr.A3067

4) Vågberg et al. (2013), Automated Determination of Brain Parenchymal Fraction in Multiple Sclerosis, Am J Neuroradiol 2012; 10.3174/ajnr.A3262

5) Ouellette et al. (2020), Validation of rapid magnetic resonance myelin imaging in multiple sclerosis, Ann Neurol. 2020 Feb 14. doi: 10.1002/ana.25705

6) McAllister et al. (2017), Quantitative Synthetic MRI in Children: Normative Intracranial Tissue Segmentation Values during Development, AJNR Am J Neuroradiol. 2017; 10.3174/ajnr.A5398

7) Vågberg et al. (2016), Brain Parenchymal Fraction in an Age-Stratified Healthy Population - Determined by MRI Using Manual Segmentation and Three Automated Segmentation Methods J Neuroradiol. 2016;43:384-391

8) Hagiwara et al. (2018), Linearity, Bias, Intra-Scanner Repeatability, and Inter-Scanner Reproducibility of Quantitative Multi-Dynamic Multi-Echo Sequence for Rapid Simultaneous Relaxometry at 3T: A Validation Study with a Standardized Phantom and Healthy Controls, Invest Radiol 2019 Jan;54(1):39-47. doi: 10.1097/RLI.0000000000000510

9) Vanderhasselt et al. (2020), Synthetic MRI of Preterm Infants at Term-Equivalent Age: Evaluation of Diagnostic Image Quality and Automated Brain Volume Segmentation, Am J Neuroradiol 2020; 10.3174/ajnr.A6533

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

The products/features in this text may not be available for clinical use on your market. Please contact us for further information.