Synthetic Brain MRI

Review of Current Concepts and Future Directions

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Abstract: Synthetic magnetic resonance imaging is a novel imaging technique that allows generating multiple contrast-weighted images based on relaxivity measurements of tissue properties in a single acquisition using a multiecho, multidelay saturation recovery spin-echo sequence. The synthetic images can be generated postacquisition from the parametric tissue maps, which can be beneficial to reduce scan time and improve patient throughput. Based on relaxometry maps, synthetic magnetic resonance imaging can also perform brain tissue segmentation and myelin quantification without additional scan time. The quantitative analysis may have implications for understanding and monitoring of the evolution of the maturation process. Similarly, the myelination process is vitally important to central nervous system functioning. Measuring myelin volume could provide relevant information for the diagnosis and treatment of patients with myelination disorders.

Key Words: brain, magnetic resonance imaging, myelin, pediatrics

SYNTHETIC MAGNETIC RESONANCE IMAGING

In conventional magnetic resonance imaging (MRI) proton signal is used to generate images.[1] An MRI examination protocol is typically composed of various sequences, which are acquired consecutively. Each sequence demands an independent acquisition with distinct parameter settings. By modifying parameters of each sequence, various contrasts are generated between tissues. The contrast of each sequence, in its turn, is dependent on the relaxation properties of the proton molecules.[2]

When each sequence acquisition is finalized, all the images obtained ought to be visually inspected and carefully analyzed to assure the desired tissue contrast is obtained. Scan duration is variable across institutions, according to the protocol. Depending upon the chosen protocol, a routine brain imaging acquisition, and imaging review may last at least from 20 up to 60 minutes.

Synthetic MRI (SyMRI) is a quantitative MRI (QMRI) technique that measures inherent T1 relaxation and T2 relaxation, which are absolute magnetic resonance properties of any living tissue. At the end of a single 6-minute scanning sequence, 2 parametric maps are generated based on magnetic properties of the tissue: R1 and R2 relaxation maps (Fig. 1 A and B). A third map that can be mathematically generated is the proton density (PD) map (Fig. 1C). A B1 uniformity correction map is generated to correct for B1 inhomogeneities (Fig. 1D). R1 map is the inverse of the T1 map, and R2 map is inverse of T2 map where units of R1 and R2 are typically 1/s, and

units of T1 and T2 are in milliseconds. SyMRI uses quantitative probing of multiple physical properties to reconstruct various contrasts from one scan.[3]

Subsequently, from those 2 maps (R1 and R2), up to 10 different contrast-weighted images can be synthetically generated (Fig. 2), each one with distinct contrast, all of them adjustable for any combination of echo time (TE), repetition time (TR), and inversion time (TI) (Figs. 3 and 4). TR, TE, and TI can be modified with mathematical inferences rather than being predetermined.[4] This is different from acquiring the images directly on the scanner with a pulse sequence where it might take an additional few minutes per acquisition with different settings.

Having up to 10 different layers of contrast in every single slice obtained gives the imaging specialist high flexibility to elect postscan the contrast weighting of their choice while decreasing the odds to recall the patient for a new visit to the radiology department.

Another byproduct of SyMRI is the possibility to perform automatic tissue segmentation and volumetric measurements of grey matter (GM) (Fig. 5A), white matter (WM) (Fig. 5B), cerebrospinal fluid (CSF) (Fig. 5D), and myelin (MYE) (Fig. 5D).[5–8]

UP TO 10 LAYERS OF CONTRAST WITH EVERY ACQUIRED SLICE

Basic SyMRI bundle includes the routinely used contrast-weighted images such as T1W, T2W, PDW, T1W FLAIR, short TI inversion recovery, and T2W FLAIR. The advanced package may also include less commonly used image contrasts such as phase-sensitive inversion recovery, phase-sensitive inversion recovery-vessel, double IR with WM suppression and double IR with GM suppression (Fig. 6). SyMRI generated contrasts have been compared to conventional imaging in multiple studies by multiple research groups in all age groups and, in consensus, SyMRI-generated image contrast has been shown to be an alternative to conventional imaging.[4,9–11] A favorable feature for imaging the developing brain is the fact that contrast images can be tailored after the actual scanning is performed.[10] Table 1 shows a comprehensive list of SyMRI-generated byproducts.

ACQUISITION SEQUENCE

The acquisition sequence for SyMRI is a multidynamic multi-echo sequence. This is a saturation recovery prepared 2D FSE and is designed to acquire raw images that are necessary for quantitative T1, T2, PD, and B1 mapping in the brain.[5] The sequence acquires images at 2 spin TEs (typically 21 and 94 ms) and 4 saturation recovery times (typically 150, 580, 2000, and 4130 ms) interleaved to generate multiple image contrasts, from which the spin parameters can be calculated (Fig. 7).

The total number of images acquired per slice is (number of saturation recovery times = 5) × (number of TEs = 2) resulting in 10 composite images per slice at different saturation delays and TEs. This sequence combines features of traditional T1 and T2 mapping in a single sequence. A least squares fit is performed on the signal
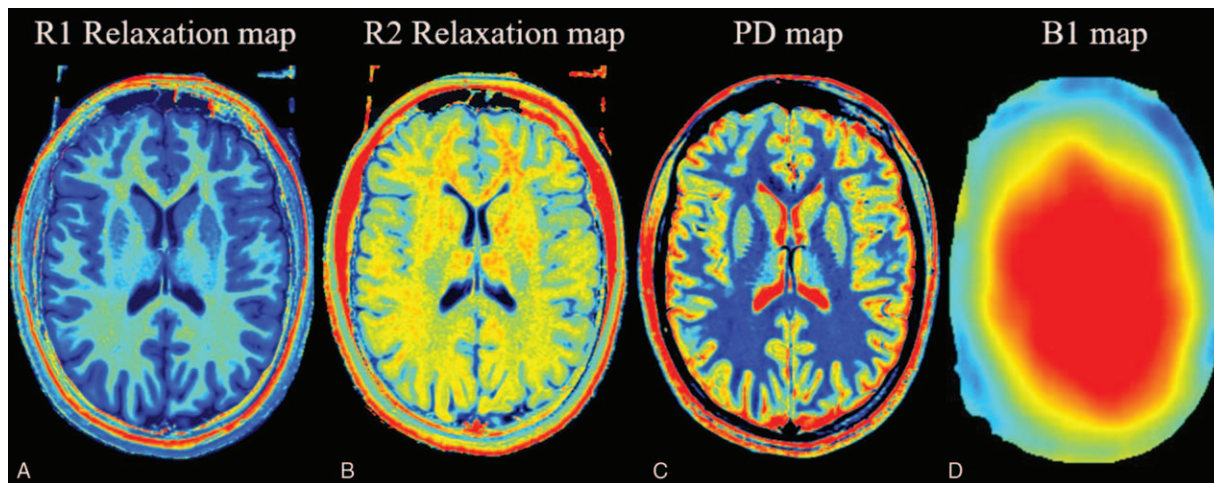
FIGURE 1. Four maps generated at the end of a 6-minute scanning sequence. R1 (A) and R2 (B) are 2 relaxation maps. PD map (C) is a mathematically generated map. A fourth map (D) called the B1 uniformity map is generated to correct for B1 inhomogeneities.

intensity of these images to estimate longitudinal and transverse relaxation rates, PD, and B1 field inhomogeneity map.[12]

POSTPROCESSING

Generation of relaxation maps and multiple contrast synthetic images, parametric maps, segmented volumes, and MYE estimation are an automatic function of SyMRI software. The digital imaging and communications in medicine images generated with the acquisition sequence feed into the software and at the output is the synthetic images, voxel-based parametric maps, segmented volumes, and MYE estimates. The software may be implemented as part of the scanner vendor product such that the images get generated within a minute of the acquisition or may be installed as a call button on picture archiving and communication system (PACS). The raw
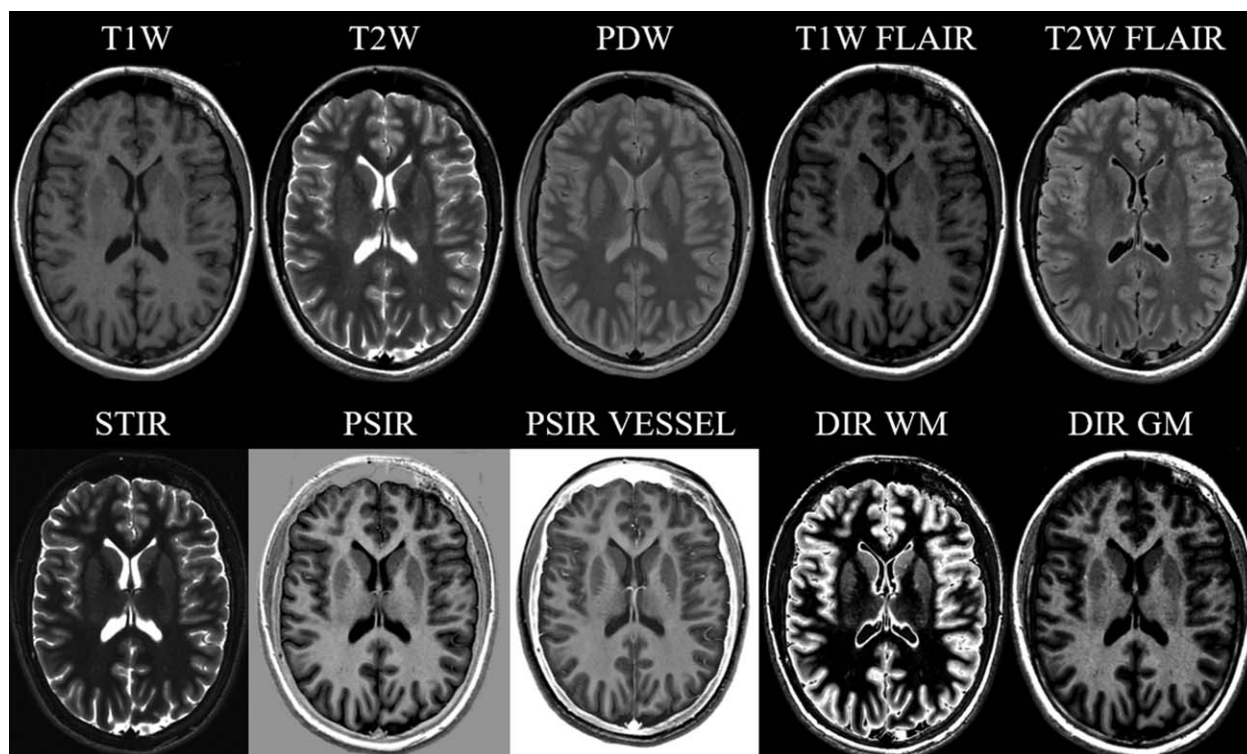

FIGURE 2. Ten images from a single healthy volunteer at the level of the basal ganglia, demonstrating the basic and advanced synthesized contrasts. Basic SyMRI bundle includes T1W, T2W, PDW, T1W FLAIR, STIR, and T2W FLAIR. Advanced bundle includes (PSIR), PSIR (vessel), DIR WM suppression and DIR GM suppression. PSIR indicates phase-sensitive inversion recovery; STIR, short TI inversion recovery.
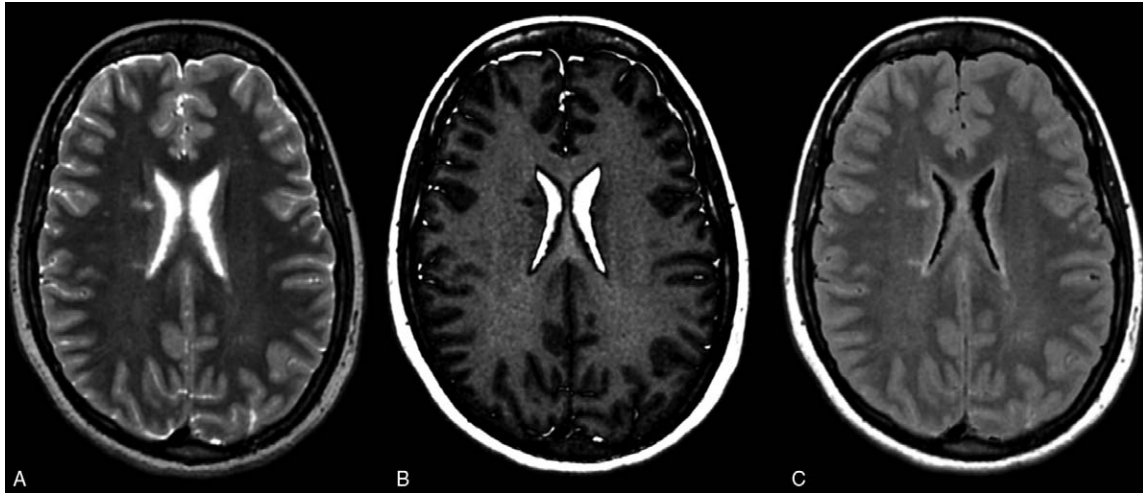
FIGURE 3. Free choice of TE, TR, and TI. Same slice position in a patient with MS lesions. With pathology-specific parameters, the ability to adjust TR/TE/TI on an already acquired dataset allows you to investigate unique sequence weighting. A, Axial midbrain slice with a $TR = 15000$ ms, $TE = 100$ ms, $TI = 100$ ms. B, Same slice $TI = 1000$ ms and (C) same slice $TI = 3000$ ms.
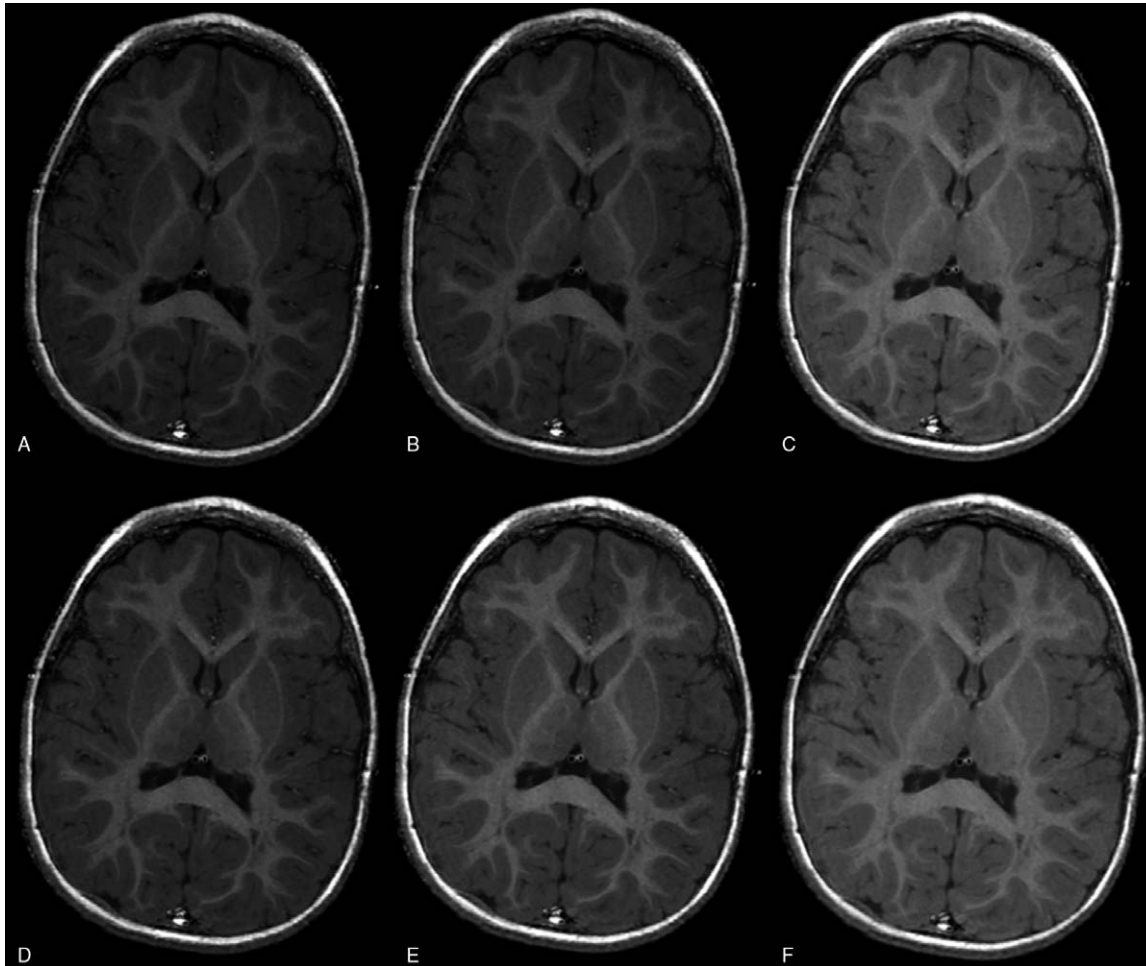

FIGURE 4. Selected images demonstrating variations of TR and TE values. A, TR/TE: 100/5 ms, (B) TR/TE: 200/5 ms, (C) TR/TE: 500/5 ms, (D) TR/TE: 100/10 ms, (E) TR/TE: 200/10 ms, and (F) TR/TE: 500/10 ms. The ability to adjust the TR and TE postacquisition and without the need to rescan may help reduce the rate of recall.
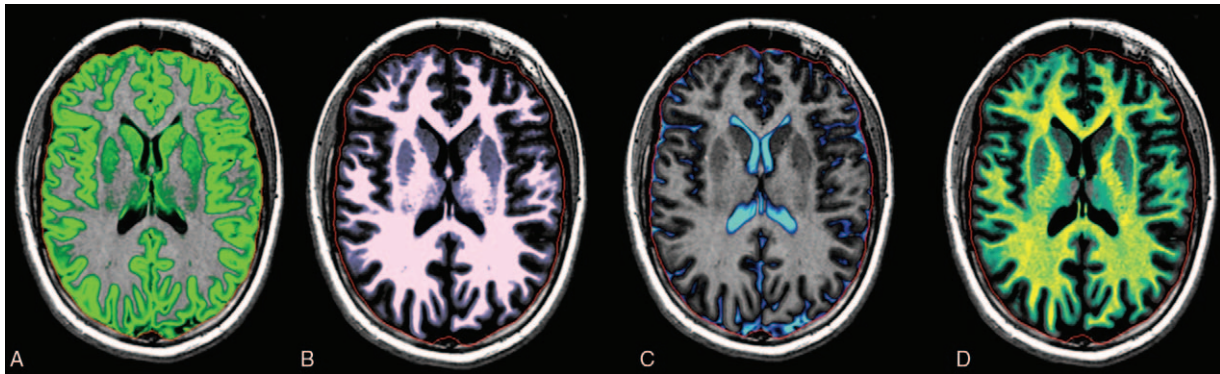
FIGURE 5. Selected images at the level of the basal ganglia, showing the automatic segmentation of grey matter (A), white matter (B), cerebrospinal fluid (C), and myelin (D).

images from the scanner are then sent to PACS, and the SyMRI software can query the images and generate the images on the PACS workstation at the call of the reading radiologist or may be installed on a stand-alone workstation or a combination of all. Representative image demonstrating the process is shown in Figure 6.

PARAMETRIC MAPPING

An inherent strength of SyMRI is the acquisition and generation of T1, T2, R1, R2, and PD maps. The sequence allows for the calculation of absolute voxelwise R1 and R2 relaxivity and PD values via SyMRI software (<60 s processing time). Using QMRI created
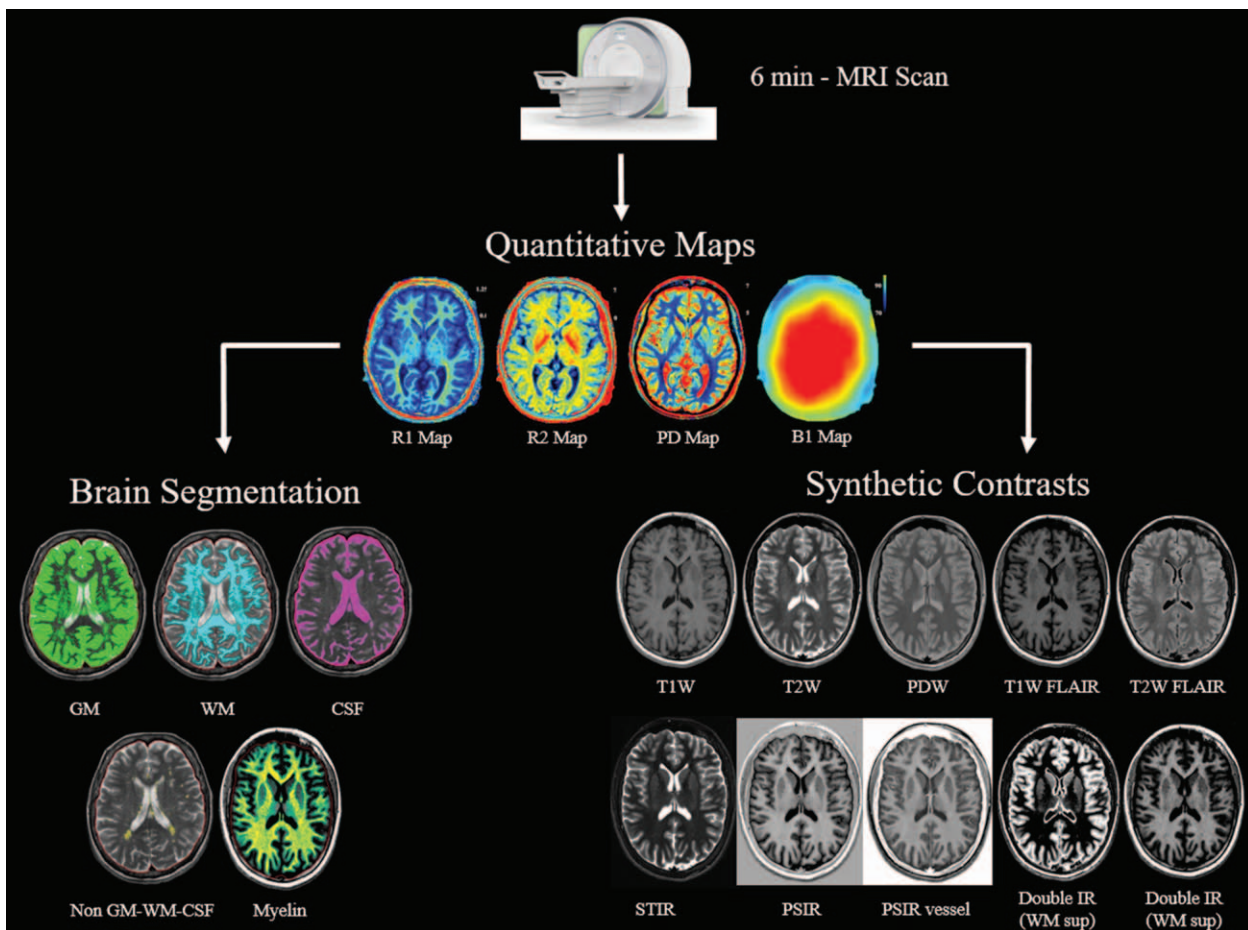

FIGURE 6. Representation of the process of synthetic imaging acquisition and postprocessed synthetic contrast images and segmented volumes. PSIR indicates phase-sensitive inversion recovery; STIR, short TI inversion recovery.

TABLE 1. SyMRI-generated Byproducts

Quantitative MAPS	Contrasts	Brain Segmentation
R1 relaxation map	T1W	White matter
R2 Relaxation map	T2W	Gray matter
Proton density map	PDW	Cerebrospinal fluid
	T1W FLAIR	Non-WM/GM/CSF
	T2W FLAIR	Myelin
	STIR	
	PSIR	
	PSIR (vessel)	
	Double IR (WM suppressed)	
	Double IR (GM suppressed)	

PSIR indicates phase-sensitive inversion recovery; STIR, short TI inversion recovery.

images without the variation in signal intensity that occurs when using conventional MRI acquisition where the contrast is dependent on the other pixel values in the image, making it possible to compare images between different examinations and different patients directly.

BRAIN SEGMENTATION

SyMRI-generated relaxivity maps can be used to perform quantitative brain segmentation and MYE quantification.[8] MRI-based brain segmentation and volume estimation of GM, WM, and CSF may be useful in several clinical and research fields.

SyMRI allows automated brain segmentation and volume estimation optimized for clinical use without manual intervention. SyMRI-based volume measurements have been compared with other segmentation software's that are typically used for research purposes and found to agree with the low repeatability measurements.[11]

IMAGE INTENSITY STANDARDIZATION

In conventional MRI there is a lack of image intensity standardization due to inherent differences in coil sensitivity, pulse sequence, and acquisition parameters. Signal intensity divergence from one examination to the next and the acquisition of different mappings from tissue properties to image intensity levels, impede direct comparison of absolute signal intensity values between examinations.[13,14]

QMRI can overthrow this inconsistency along with an accurate appraisal of the physical characteristics of the tissue namely longitudinal R1 relaxation rate, the transverse R2 relaxation rate, and the PD.

QUANTITATIVE DATA

Within the SyMRI software, there are multiple measuring tools. It is possible to measure tissue volumes in a region of interest defined by the user. The brain parenchymal fraction is a ratio based on intracranial volume, brain tissue, and CSF.[15,16]

MYE calculation and segmentation can also be performed.[17] This feature could be potentially applied in patients with disorders affecting the MYE.

PATIENT THROUGHPUT ACCELERATION

Betts et al could save six and half minutes of scanning time in the first attempt to implement SyMRI to evaluate the central nervous system (CNS) of pediatric patients. The group studied 30 patients, who underwent conventionally and SyMRI at the same examination. The time to obtain SyMRI sequence was of 6 minutes where the total amount of time to acquire the conventional sequences was 12.5 minutes.[9] According to them, a synthetic acquisition could be used to replace standard multiecho T1, T2, FLAIR, and PD sequences in screening MRI studies, which could subsequently grant additional time for targeted evaluations.[9]

The possibility to achieve all-in-one sequences during a single acquisition may have a positive impact on pediatric brain imaging,
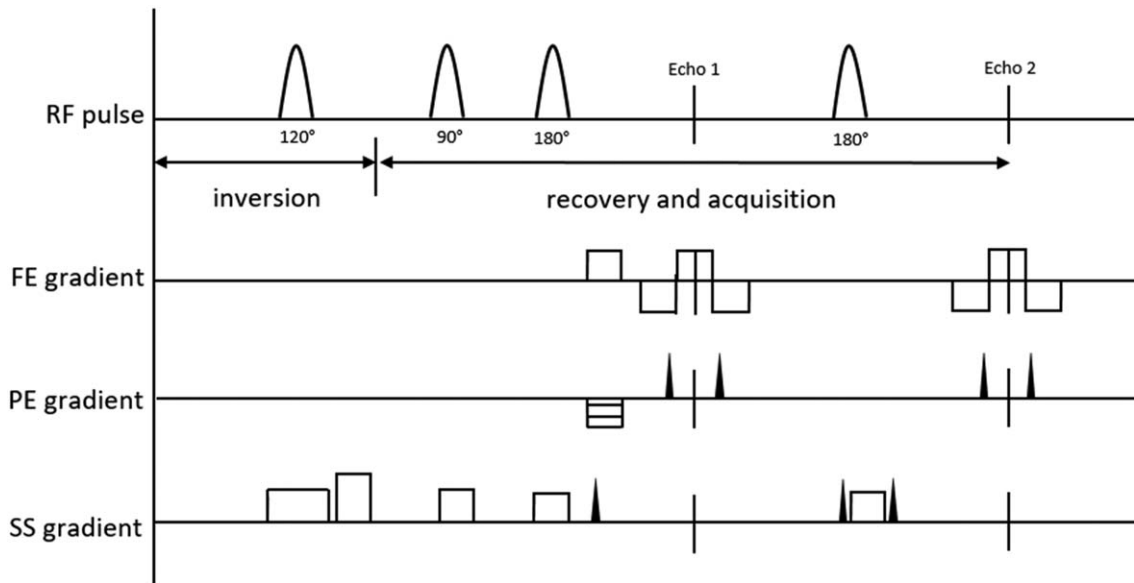
RF = radiofrequency; FE = frequency encoding; PE = phase encoding; SS = slice selection

FIGURE 7. Multidynamic multi-echo (MDME) acquisition sequence for SyMRI. FE indicates frequency encoding; PE, phase encoding; RF, radiofrequency; SS, slice selection.

potentially decreasing the number of studies requiring general anesthesia, and thus preventing potential long-term complications on the developing brain of children.[18–20] Another group of individuals who could benefit from SyMRI are patients with claustrophobia.

REDUCED RISK OF A RECALL BUT INCREASED RISK OF FAILURE

Since the contrast-weighted images are synthesized, any combination of TE, TR, and TI can be entertained without re-examining the patient. The scanner settings can also be altered after the completion of the examination, granting the possibility to reach the optimal contrast weighting for that particular subject. The ability to readjust contrast weightings is particularly useful among pediatric patients because it is especially challenging to know the optimal scanner settings for a brain in development. On the contrary, if the SyMRI acquisition fails, for example, due to motion, the artifact will propagate to the entire set of images.

EFFICIENT SCREENING PROCEDURE

Abbreviated scan times opens up the possibility of using MRI as a screening tool for a wide spectrum of CNS pathologies. Diagnostic accuracy and quality of synthetically generated sequences are comparable to those conventionally acquired. West et al performed a study to determine the diagnostic accuracy of SyMRI compared with conventional sequences in pediatric patients. Synthetic axial T1, T2, and T2 fluid attenuation inversion recovery or PD-weighted sequences were acquired to match the comparable clinical sequences.[10]

It is important to bear in mind that SyMRI is unable to provide the same spatial resolution of a 3D sequence. Third-level pediatric centers are already using 3D isometric isotropic imaging. Furthermore, 3D images can be reformatted without losing anatomical resolution.

USING SYNTHETIC MAGNETIC RESONANCE IMAGING IN EVALUATING THE MYELIN IN CHILDREN

Myelination process is an essential step for the CNS development. This process is faster during the first 2 years of life, and it continues throughout childhood and adolescence.[21]

MYE maturation is associated with shortening of T1 and T2 relaxation times, reduction of water diffusion and PD, and increased anisotropy and magnetization transfer.[22] Current MRI techniques use a combination of T1 weighting, T2 weighting, FLAIR, diffusion tensor imaging, susceptibility, and magnetic resonance spectroscopy as an indirect biomarker to provide qualitative and quantitative information regarding MYE content.[23–26]

SyMRI estimates MYE partial volume as part of a multicomponent partial volume model in each acquisition voxel.[27] MYE is estimated using a model that divides each acquisition voxel into 4 compartment models, MYE partial volume, cellular tissue partial volume, free water, and bound water partial volume.[27]

A recent study by McAllister et al[16] has evaluated whole-brain normative MYE segmentation values during development, using SyMRI. According to this study, estimation of myelination status is comparable across MRI and SyMRI.[16] Quantitative assessment of MYE volume, however, has the potential to improve myelination staging and disease assessment.

FUTURE RESEARCH DIRECTIONS: A HYPOTHETICAL ROLE FOR SYNTHETIC MAGNETIC RESONANCE IMAGING IN PEDIATRIC BRAIN IMAGING

Diagnosing WM diseases is not always straightforward, and a precise diagnosis is commonly achieved in a later stage of the disease. According to an MRI-based approach to the diagnosis of WM disorders, the first step is to define whether the abnormal MRI WM changes are due to hypomyelination or not.[28]

Pelizaeus-Merzbacher and Pelizaeus-Merzbacher-like diseases are the most frequent hypomyelinating disorders (HMDs). Despite the progress in the understanding of this group of pathologies, HMDs represents the largest category of undiagnosed genetic leukoencephalopathies.[28,29] Since the advent of MRI, HMDs have been mainly evaluated by visual assessment of T1- and T2-weighted images.[30] An HMD is suspected in cases in which MRI depicts significant delay of myelination compared with normal standards.[30,31] SyMRI could be used as an additional tool in the baseline and follow-up quantification of MYE affected disorders.

In general, MRI segmentation and volume estimation is not used for clinical practice because segmentation and estimating volumes is not a trivial task. The ability to automatically perform brain segmentation and estimate brain volumes offer potential clinical applications for pediatric neurological studies. The measured pathological changes can be applied to surgical planning and image-guided interventions.

CONCLUSIONS

SyMRI is now available for clinical use and is a promising for pediatric clinical applications. Although sedation is routinely used in young children, SyMRI has the potential to be used as a screening tool in children not requiring sedation and in those requiring shorter scan times. Studies are needed to assess the benefits of using SyMRI in decreasing anesthesia or sedation time in children and its application in evaluation of patients with MYE disorders.

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