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RESEARCH ARTICLE

A standardised method for measuring magnetisation transfer ratio on MR imagers from different manufacturers—the EuroMT sequence

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Abstract Magnetisation transfer ratio (MTR) is increasingly used to evaluate neurological disorders, especially those involving demyelination. It shows promise as a surrogate marker of disease progression in treatment trials in multiple sclerosis (MS) but the value measured is highly dependant on pulse sequence parameters, making it hard to include the technique in large multi-centre clinical trials. The variations can be reduced by a normalisation procedure based on the flip angle and timing of the presaturation pulse, but correction for parameters such as saturation pulse shape, amplitude, duration and offset frequency remains problematic. We have defined a standard pulse sequence, to include a standard presaturation pulse and set of parameters, which can be implemented on scanners from both General Electric and Siemens, and has also been used on Phillips scanners. To validate the sequence and parameters, six European centres measured MTR in the frontal white matter of normal volunteers. It was possible to measure MTR values in controls which were consistent to within approximately ±2.5 percentage units across sites. This degree of precision may be adequate in many situations. The remaining differences between sites and manufacturers are probably caused by B_1 errors.

Keywords Magnetisation transfer · Pulse sequence design

Introduction

Since its introduction by Wolff and Balaban in 1989 [1], the measurement of magnetisation transfer ratio (MTR) has increasingly been used to evaluate neurological disorders [2–4], especially those involving demyelination [5–12]. Unfortunately, while the value of MTR measured at a particular institution may be very reproducible [13], its absolute value is highly dependant on scanner and pulse sequence parameters including TE, TR and the number of slices. An alternative to the use of a simple ratio, which overcomes these pulse sequence dependencies, is to develop models which relate the measured MT signal change to underlying parameters, such as bound proton fraction, relaxation times and transfer rates [14]. Models are only now becoming available [15–19] to describe the pulsed, off-resonance irradiation used in clinical sequences completely, and the large number of measurements needed for such model-based approaches may limit clinical utility.

We have previously shown [20] that the variations in MTR between different sites and pulse sequences can be reduced by a normalisation procedure based on the flip angle of the presaturation pulse and the time between saturation pulses, TR′, (typically TR/(number of slices)). Significant inter-site variation remains, however, as the normalisation makes no correction for saturation pulse parameters such as shape, amplitude, duration and offset frequency. We have therefore defined a standard pulse sequence, a standard presaturation pulse and a set of standard pulse sequence parameters that should be implementable on most commercial scanners. Although this sequence has not been optimised, a reasonably high value of MTR (about 40 percent units in white matter) is obtained. We have produced reference implementations of the sequence for GE Signa scanners (General Electric Medical Systems, Milwaukee, USA) and Siemens Magnetom scanners (SP and Vision; Siemens Medical Solutions, Erlangen, Germany). To validate the sequence and parameters, six European centres measured MTR in the frontal white matter of normal volunteers. A preliminary account of this work has already been given [21]. In addition the sequence has also been implemented on scanners from Philips Medical Systems [22]. It is the basis of recent European multi-centre work [23] which showed complete elimination of inter-centre differences.

Methods

Pulse sequence

A 2D gradient echo sequence was chosen for the underlying pulse sequence in order to minimise MT effects due to off-resonant saturation by 90 and 180° spin-echo imaging pulses. For Siemens scanners the basic sequence was *fast imaging with steady-state precession (FISP)*; for GE it was *gradient-recalled acquisition in the steady state (GRASS)*. To ensure a relatively 'pure' PD-weighted MT contrast, the excitation (imaging) flip angle, α, and the TR and TE were chosen to give minimal T_1 and T_2-weighting effect in grey/white matter. TE was the smallest value for which both scanner types perform full k-space acquisition (GE – no *fractional echo*). Complete sequence parameters are given in Table 1.

The MT pulse, which was applied before each excitation (imaging) pulse, was a Gaussian shape, with a duration of 7.680 ms and a bandwidth of 250 Hz, and was applied 1.5 kHz off-resonance (on the opposite side of the water resonance to fat). Its full-width-half-maximum was 3.512 ms, and it had the analytic form $\exp(-0.2248\,t^2)$, with t in ms. The amplitude of the pulse, which was defined by the nutation angle the pulse would provide if applied on resonance, was set to 500°. We refer to this as the effective flip angle, θ_{sat}, of the saturation pulse. The pulse used is standard on Siemens Vision scanners; it was implemented by one of the authors (WGS) for the Siemens SP systems, and by another of the authors (GJB) for the GE scanners. (In the latter case the pulse was added to a locally modified pulse sequence.) The MT pulse flip angle was chosen so that, for the TR and number of slices used, the sequence remained within the SAR limits of all countries involved in the study.

The MTR values produced by the EuroMT pulse sequence can be approximately predicted using a continuous wave (CW) approximation binary spin-bath model [15–19]. To calculate the value of the CW power-equivalent RF field, the values of the pulse shape parameters [15–19] p_1=0.48186 and p_2=0.34409 are required.

Scanning

Imaging was performed at 1.5 T. For all scanners, the manufacturers' standard transmit/receive head coils were used. Two normal controls were imaged at each of six sites (four with Siemens, six with GE scanners). At all but one site, each volunteer was scanned twice, at least 24 h apart. All volunteers gave informed consent according to the rules of the scanning site.

We have previously shown [20] that when other parameters are fixed, the MTR value is largely determined by the effective nutation rate (ENR), defined as the effective flip angle of the saturation pulse, θ_{sat}, divided by the time between the start of successive saturation pulses, TR′. At each examination three sequence variations were performed with different values of ENR (see Table 2):

a) *with* $ENR = 12.5\,\mathrm{deg}\,ms^{-1}$: two measurements were performed consecutively, with identical slice positioning, an MT pulse flip angle of 500°, and other parameters as listed in Table 1. The first measurement was made without MT pulses (M_0), the second with MT pulses (M_{sat}). Transmitter gain and receiver attenuators were kept constant between scans. On the GE scanner this is automatic, due to the pulse sequence design. On the Siemens machines the first measurement was performed with automatic adjustments, and for the second measurement the same parameters were entered manually. This ENR value was chosen to be about the highest that could be obtained within the SAR limitations.

Table 1 Pulse sequence parameters used for all scans

Siemens parameter name	GE parameter name	Value
TR (ms)	TR (ms)	960
TE (ms)	TE (ms)	12
α pulse flip angle	α pulse flip angle	20°
MT pulse flip angle	MT pulse flip angle	500°(a, c), 400°(b)
FOV	FOV	240 mm
Matrix size	Matrix size	128×256
# of slices	# of slices	24(a, b), 16 (c)
Slice thickness (mm)	Slice thickness (mm)	5
Orientation	Orientation	Oblique axial
# of acquisitions	NEX	2
# of acquisitions	# of acquisitions	2
Readout bandwidth	Readout bandwidth	Siemens – 130 Hz/point (33.28 kHz); GE – 32 kHz; (125 Hz/point)
GMN	Flow compensation	On
Swap readout/phase encoding direction	Swap phase/frequency	No
Oversampling	N/A	No
Series	N/A	Interleaved
Filter	N/A	Off
Interpolation	N/A	Off

The three sequences (a, b, c) are defined in Table 2

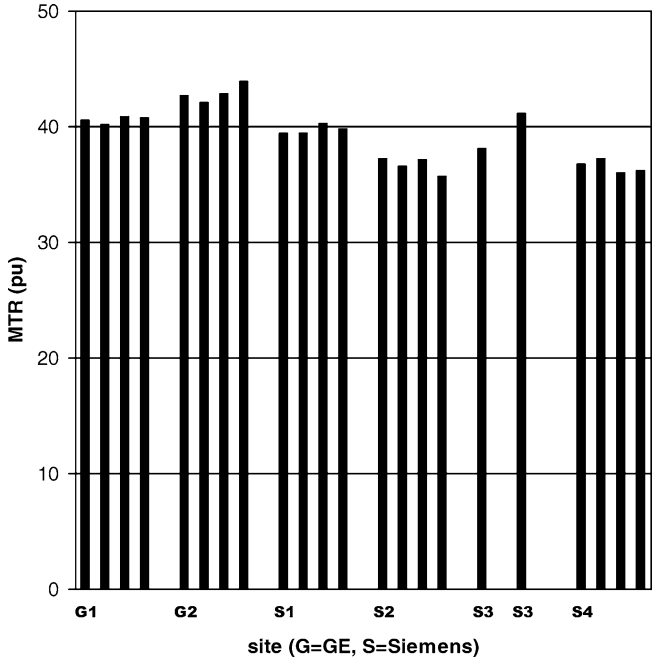

Fig. 1 Magnetisation transfer ratio values of white matter in normal controls at the six sites, for sequence (a) (the most powerful). For each site except S3, the four bars represent a subject with two scans, then a second subject also with two scans. Site S3 had two subjects but no repeats. Sites G1 and G2 had the same subjects

b) *with* $ENR = 10.0\,\mathrm{deg}\,ms^{-1}$: another measurement was made with a reduced MT pulse flip angle of 400°. On the GE scanners a second measurement of M_0, without MT pulses, was also performed.

Table 2 Sequence information and MTR values

Sequence	*a*	*b*	*c*
θ_{sat} (deg)	500	400	500
TR′ (ms)	40	40	60
Number of slices	24	24	16
ENR[c] ($\mathrm{deg\,ms^{-1}}$)	12.5	10.0	8.33
MTR[a] (pu)	39.3 (2.5)[b]	32.3 (2.9)	30.4 (3.0)

[a]mean value (standard deviation) in frontal white matter, over all subjects and scanners, pu = percent units
[b]for sequence (a), scanner-specific mean values were: GE: 41.7 pu, Siemens: 37.9 pu
[c]*ENR* effective nutation rate = θ_{sat}/TR′

c) *with* $ENR = 8.33\,\mathrm{deg}\,ms^{-1}$: finally, a measurement was made with an MT pulse flip angle of 500° but with only 16 slices, to increase TR′, the delay between repetitions of the saturation pulse, from 40 ms to 60 ms. On the GE scanners an M_0 measurement was again performed.

The subjects were positioned in the scanner and landmarked to the 'nasion' using the patient-positioning lights in the usual way. Special care was taken, however, to ensure that the position of the head was consistent across all subjects. In particular, the position of the nasion reference point relative to the head coil was kept constant for all subjects, in order to minimise the effects of RF inhomogeneity, which can lead to a noticeable spatial dependence in the saturation pulse amplitude, and thus measured MTR, along the coil axis [24]. After localising images, oblique axial slices were prescribed as per Table 1. In all cases,

slice positions were adjusted to give at least one slice through frontal white matter.

For all scans, signal intensity, S, and standard deviation (SD) were evaluated using manufacture-provided software in identical regions of interest (ROIs) in each M_{sat} and M_0 image. The MTR was then calculated using the usual formula, $MTR = 100 (S_0 - S_{sat}) / S_0$. Measurements on controls were made on an area of right frontal white matter using the largest ROI possible without including partial volume pixels from other tissues.

The statistical analyses were undertaken using mixed effects analysis of variance. The variation in MTR values was modelled as being caused by two fixed effects (scanner manufacturer and ENR) and three random effects. The random effects were inter-site variation (i.e. variation between different scanners from the same scanner manufacturer), inter-subject variation (measured at the same site) and intra-subject variation (variation over repeated measurements at the same site). ENR was treated as a categorical variable. The scanner manufacturer, ENR and random effects were assumed to have additive effects on the value of MTR (i.e. statistical independence was assumed between all components of variation).

Results

Mean MTR values in the white matter of normal controls are shown in Table 2. All three sequences behaved similarly in terms of inter-subject, inter-site and inter-manufacturer variation. MTR values for sequence a) are shown graphically in Fig. 1. Intra-subject (scan–rescan) reproducibility was reasonable good; for subjects measured at the same site the root-mean-square difference in MTR values was 1.5 pu (range 0.0–4.5 pu; $n = 30$). Given the relatively small effect of ENR, the assumption that scanner and random effects are independent of ENR was reasonable.

The observed difference between the two scanner types was 4.0 pu (standard error, SE = 1.5 pu; across all three sequences), with GE being higher than Siemens. Although MTR increased with ENR, a linear model for MTR versus ENR did not fit well. The estimated inter-site SD was 1.5 pu (variance 2.3, SE of variance 1.9); the estimated inter-subject SD was 1.2 pu (variance 1.6, SE of variance 1.0); the estimated intra-subject SD was 1.0 pu (variance 1.1, SE of variance 0.21).

Discussion and conclusions

We have described a pulse sequence which can be implemented on scanners from more than one manufacturer and which provides MTR measurements over the whole brain in approximately 6 min. By careful choice of parameters it is possible to measure MTR values which are consistent to within approximately ±2.5 pu across multiple sites. This degree of precision may be adequate in many situations; multiple sclerosis (MS) lesions, for instance, typically differ in MTR from the surrounding normal appearing white matter (NAWM) by between 15 and 90%.

The remaining differences between sites and manufacturers may be due to several factors:

i) MTR is highly dependant on the precise presaturation pulse flip angle, and thus on B_1 calibration. On clinical scanners, such as those in this study, this calibration is usually part of the automatic scan setup procedure and is not under direct operator control and is intended to give precise (i.e. reproducible), rather than accurate (i.e. close to the required absolute flip angle), results. The algorithm used for setting the power of RF pulses is scanner dependent, and is likely to be set up to give acceptable image quality rather than an accurate value of flip angle. King et al. [25], for example, describe a GE procedure which gives 'more uniform intensity in spin-echo images' than other methods. Brookes et al. [26] have shown that the RF flip angle on a 0.95-T Siemens Impact system can be 13.5% less than that requested; only a 4–5% difference in the flip angle calibration is needed to explain the differences we have found between scanners.

ii) MTR is very sensitive to B_1 inhomogeneity and will therefore depend on subject positioning within the head coil, to an extent determined by the homogeneity of this coil [22, 27]. Corrections for B_1 variation can be made [23, 28]. A bird-cage head coil [22] or a body transmit coil [22, 27] seem to give best B_1 uniformity.

iii) Variations in ROI positioning and MTR calculation procedure between sites may also lead to differences in reported MTR values. The variation between manufacturers may also be due to slight differences in pulse shape (e.g. due to apodisation), along with systematic differences in coil homogeneity.

Further investigation is required to determine which of these factors is significant (and how to standardise or correct for them).

In conclusion, the EuroMT sequence forms the basis for multi-centre MTR studies and is available on imagers from three major manufacturers. The most likely residual sources of inter-site difference are B_1 errors, and in a recent multi-centre MAGNIMS study [23], when the current sequence was combined with B_1 mapping and correction, inter-site differences were rendered insignificant.

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