A STUDY ON THE IMPROVEMENT OF INHERENT AND ENHANCED TISSUE CONTRAST IN MR IMAGING USING MAGNETIZATION TRANSFER AND SPIN LOCK TECHNIQUES

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The thesis is based on the following publications which are referred to in the text by roman numerals:


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SYMBOLS AND ABBREVIATIONS

\( \alpha \) \hspace{1cm} \text{flip angle}

\( \gamma \) \hspace{1cm} \text{gyromagnetic ratio}

\( \mu \) \hspace{1cm} \text{magnetic moment}

\( \theta \) \hspace{1cm} \text{angle between } B_{\text{eff}} \text{ and z-axis}

\( \tau \) \hspace{1cm} \text{correlation time}

\( \omega_0 \) \hspace{1cm} \text{angular frequency of } B_0

\( \omega_1 \) \hspace{1cm} \text{angular frequency of } B_1

\( B_0 \) \hspace{1cm} \text{static magnetic field}

\( B_1 \) \hspace{1cm} \text{oscillating magnetic field}

\( B_{1L} \) \hspace{1cm} \text{locking field}

\( B_{\text{eff}} \) \hspace{1cm} \text{effective field}

\( B_s \) \hspace{1cm} \text{amplitude of the MT pulse}

BSA \hspace{1cm} \text{bovine serum albumin}

BPP \hspace{1cm} \text{Bloembergen Purcell Pound}

CNR \hspace{1cm} \text{contrast-to-noise ratio}

CW \hspace{1cm} \text{continuous wave}

DTPA \hspace{1cm} \text{diethylenetriaminepenta-acetate}

\( F_s \) or \( \Delta \) \hspace{1cm} \text{frequency offset of the MT pulse}

\( g_i (2\pi\Delta) \) \hspace{1cm} \text{line-shape for } i \text{ spins}

Gd \hspace{1cm} \text{gadolinium}

GRE \hspace{1cm} \text{gradient echo}

Hz \hspace{1cm} \text{hertz}

IR \hspace{1cm} \text{inversion recovery}

\( K_f \) or \( R_{AB} \) \hspace{1cm} \text{cross-relaxation rate from A spin to B spin}

\( K_{\text{app}} \) \hspace{1cm} \text{apparent cross-relaxation rate}

\( M_0 \) \hspace{1cm} \text{equilibrium value of magnetization}

\( M_s \) \hspace{1cm} \text{steady state magnetization after MT pulse}

\( M_e \) \hspace{1cm} \text{steady state magnetization with off-resonance SL pulse}

MRI \hspace{1cm} \text{magnetic resonance imaging}

MT \hspace{1cm} \text{magnetization transfer}

MTC \hspace{1cm} \text{magnetization transfer contrast}

MTR \hspace{1cm} \text{magnetization transfer ratio}

NMR \hspace{1cm} \text{nuclear magnetic resonance}

NMRD \hspace{1cm} \text{nuclear magnetic resonance dispersion}

\( r_1 \) or \( r_2 \) \hspace{1cm} \text{longitudinal or transverse relaxivity}

\( R_A \) or \( R_B \) \hspace{1cm} \text{longitudinal relaxation rate of the A or B spin without cross-relaxation}
\( R_{\text{RFi}} \) rate at which longitudinal magnetization is lost due to the direct effects of the off-resonance irradiation

RF radio frequency

SE spin echo

SAR specific absorption rate

SBM Solomon-Bloembergen-Morgan

SL spin lock

SL_{\text{eff}} spin lock effect

T tesla

\( T_1 \) spin lattice or longitudinal relaxation time in laboratory frame

\( T_2 \) spin-spin or transverse relaxation time

\( T^*_{\text{2}} \) transverse relaxation time including the effect of \( B_0 \) inhomogeneity

\( T_{\text{1sat}} \) relaxation time with MT pulse

\( T_{1p} \) longitudinal relaxation time in on-resonance rotating frame

\( T^*_{1p} \) relaxation time in off-resonance rotating frame

TE echo time

TI inversion time

TL locking time

TR repetition time

\( T_s \) duration of MT pulse
INTRODUCTION

Magnetic resonance imaging (MRI) has conventionally used the T₁ and T₂ relaxation times and proton density of tissue water to produce contrast. Magnetization transfer (MT) and spin lock (SL) are techniques that offer new methods for modifying tissue contrast and improving tissue characterization in MR imaging (4, 43, 107, 110, 124).

Biological tissues contain separate populations of hydrogen protons: a highly mobile (free) hydrogen pool, and an immobile (restricted motion, mostly macromolecules) hydrogen pool. Exchange of magnetization between the free and restricted hydrogen protons is the basis of MT; MT is an indirect process mediated by macromolecules. The macromolecules also have an effect on the observed SL contrast but the presence of macromolecules is not necessary for the SL effect to occur (116). Moreover, it has been suggested that at a very low field strength MT is the main source of relaxation observed with the SL technique (14).

MT and SL imaging are generated by using a preparation pulse followed by a conventional imaging sequence. In the on-resonance SL experiment the magnetization decays along the RF field, $B_{1L}$, whereas the magnetization decays along the effective field, $B_{\text{eff}}$, at angle $\theta$ to the static field, $B_0$, in the off-resonance SL or MT experiment.

Gadolinium based contrast agents are frequently used to increase the sensitivity and specificity of brain tumour studies (27, 106). An increase in contrast of brain images may be achieved by increasing the contrast agent doses (100). Synergistic enhancement with gadolinium and MT has been demonstrated in clinical imaging (32, 67, 84, 90). Also, a near resonance SL pulse used in conjunction with gadolinium has shown a potential to improve visualization of enhancing lesions (115).

One purpose of this study was to evaluate and optimize the effect of the simultaneous use of a paramagnetic contrast medium and MT, and on-and off-resonance SL imaging. The other purpose was to study the possibility of characterizing the head, neck and brain tissues with SL and MT relaxation parameters and to optimize image contrast.
REVIEW OF THE LITERATURE

1 Nuclear magnetic resonance

1.1 Principle of nuclear magnetic resonance

The phenomenon of nuclear magnetic resonance (NMR) was first proposed and demonstrated by Bloch (8) and Purcell et al. (96). Since then, NMR has had a tremendous impact on chemistry, physics, and other disciplines. The physical principle that forms the basis of NMR is the interaction of nuclei, which have a non-zero magnetic moment, with a magnetic field. The most important of such nuclei is the proton, the $^1H$ nucleus, because of its large natural abundance (almost 100%), high magnetic moment and high physiological concentration. A nucleus possesses an angular momentum and its own intrinsic magnetic moment ($\mu$). When $\mu$ is placed in a static magnetic field, $B_0$, it will experience a torque which results in precession around the axis of the magnetic field ($z$-axis). The angular frequency, $\omega_0$, is proportional to $B_0$ as given by the Larmor equation:

$$\omega_0 = \gamma B_0$$  \hspace{1cm} (1)

where $\gamma$ is the nuclear gyromagnetic ratio. If an oscillating magnetic field, $B_1$, (RF pulse) at the Larmor frequency oriented in the xy plane is applied, $\mu$ will experience a second torque which will rotate it into the xy plane. In a sample comprising many nuclei, the xy component of the net magnetic moment ($M$) will give a measurable signal.

According to quantum mechanics, when a nucleus is placed in a magnetic field the nucleus may assume one of $2I + 1$ possible energy states, where $I$ is the spin quantum number. Because hydrogen has a spin quantum number of $\frac{1}{2}$ it is found in one of two states having energies

$$E = \pm \mu B_0$$  \hspace{1cm} (2)

When we irradiate the proton with an RF pulse with energy equal to the separation of the two energy levels ($2 \mu B_0$) a quantum of energy is absorbed and transition takes place from the lower state to the upper state.

It is possible to use classical mechanics to describe many aspects of NMR. Thus a set of classical equations describing a group of nuclei in a magnetic field was derived by Bloch (8):
\[ \frac{\partial M}{\partial t} = \gamma M x B_0 + \gamma M x B_1 - \frac{i M_x + j M_y}{T_2} - k \frac{M_z - M_0}{T_1} \] (3)

The first and second terms represent the precession and perturbation (energy absorption), respectively. The third and fourth terms represent longitudinal or spin-lattice relaxation (T1) and transverse or spin-spin relaxation (T2), respectively. The Bloch equations are based on the assumptions that the interaction of the spins with the lattice and with each other can be considered independently of their interaction with the externally applied magnetic field, B0, and that the approach to M0 and the decay of Mx and My can be described as first order rate processes (i.e. exponential approach to equilibrium). This appears to be a valid assumption for mobile environments, as in liquids, in which the correlation time of the nuclei is short compared to the Larmor period, but not for solids.

1.2 Magnetic resonance imaging

In magnetic resonance imaging (MRI) strong external linear magnetic field gradients are applied across the imaging region. Thus different points in space become identified by different resonance frequencies, which allows the location of nuclear spins emitting RF fields to be determined by their frequency. The magnetic field gradient is applied independently of the static field by means of a specially shaped coil. When a linear gradient (Gx) is applied, the Larmor frequency will depend on the position along the x axis as shown by:

\[ \omega = \gamma B_0 + \gamma G_x x \] (4)

Lauterbur (71) and Mansfield and Grannell (81) were the first to propose, independently, the use of proton NMR to produce magnetic resonance images. Their approach forms the basis for most modern MR imaging instruments. The application of MR imaging to medicine has had an enormous impact on diagnostic radiology. Medical images can be routinely and non-invasively generated at any angle to the human body. The NMR signal not only provides morphological data, but also in vivo data reflecting human biochemistry and pathophysiology.
1.3 Longitudinal and transverse relaxation

For liquid water, the $1/T_1$ and $1/T_2$ relaxation rates can be described by the equations derived from the theory of Bloembergen, Purcell and Pound (BPP) (9), with the assumption of isotropic rotation for which the correlation function decays exponentially, as follows:

$$\frac{1}{T_1} \propto K \left[ J(\omega_0) + J(2\omega_0) \right]$$  \hspace{1cm} (5)

and

$$\frac{1}{T_2} \propto K \left[ J(0) + J(\omega_0) + J(2\omega_0) \right]$$  \hspace{1cm} (6)

where $K$ is a constant that includes a number of nuclear parameters and another constant. $J(\omega_0)$ is the spectral density function which can be defined as the Fourier transform of the correlation function. Longitudinal relaxation describes the transfer of energy from the spin system to the lattice in order to re-establish thermal equilibrium of the nuclear spin system. The magnetic field fluctuations that have Fourier components at $\omega_0$ and $2\omega_0$ are capable of inducing energy transfer between the spin system and the lattice. Transverse relaxation involves the nuclear exchange energy one with another, the net effect being a reduction of the magnetization in the transverse plane. The Fourier components of molecular motions at zero, $\omega_0$ and $2\omega_0$ are capable of inducing energy exchange between spins.

If a strong $B_{1L}$ field ($B_{1L} > B_{\text{local}}$), where $B_{\text{local}}$ is the local field, is applied in the plane transverse to the direction of $B_0$ then we can define a longitudinal relaxation rate in the rotating frame $1/T_{1\rho}$ as follows:

$$\frac{1}{T_{1\rho}} \propto K \left[ J(\omega_1) + J(\omega_0) + J(2\omega_0) \right]$$  \hspace{1cm} (7)

The magnetic field fluctuations that have Fourier components at $\omega_1$, $\omega_0$ and $2\omega_0$ are capable of inducing energy transfer between the spin system and the lattice.

The BPP theory is inadequate for describing the relaxation of a complex structure such as human tissue because tissue is heterogeneous, consisting of water and macromolecules, and the molecular motion cannot be described with a single correlation time. Several models have been introduced to describe the state of water in heterogeneous protein systems, such as tissues (15, 49, 58).
2 Relaxation in biological systems

2.1 Protein-water interaction

In liquid water, protons are relaxed by interactions between the magnetic dipoles of protons of the same molecules (intramolecular) and also those of neighbouring water molecules (intermolecular), the hydrodynamic interaction, (15, 58). In a solution of native protein, water protons are relaxed predominantly by other water protons. For immobilized protein and for tissue, those interactions that transfer proton magnetization between solute and solvent predominate. The presence of macromolecules enhances relaxation of water protons through a hydrodynamic effect and a cross-relaxation effect. Cross-relaxation, the transfer of magnetization between protein and water protons, was first reported by Edzes and Samulski in hydrated collagen and muscle tissue (26).

The protein becomes immobilized when the Brownian reorientation of the protein is comparable to the Larmor precessional frequency of a protein proton in the field of its neighbor (≈20 kHz) (58). When protein is immobilized, relaxation of its protons is no longer described by a motional narrowing condition. The mechanisms that permit efficient communication between the protein protons and the water protons when the protein is immobilized (not rotating freely) are the same as those in protein solutions. The fundamental difference is the efficient dipolar coupling among protons in the immobilized protein system that makes spin diffusion efficient and makes the whole protein-proton population respond collectively. At low fields (≤ 20 MHz) in immobile protein there are comparable contributions to 1/T1 from hydrodynamic and cross-relaxation mechanism. At higher fields, although cross-relaxation is relatively frequent in immobile protein it contributes little to 1/T1 (61). The water proton 1/T1 nuclear magnetic resonance dispersion (NMRD) profiles of many tissues are similar to each other and to those of immobilized protein (58, 78). The behaviour is quite similar whether the protein is immobilized e.g. by thermal denaturation or chemical cross-linking.

2.2 Models for cross-relaxation

There are two models for cross-relaxation (Fig. 1) which emphasize the role of proton chemical exchange between protons of water and exchangeable protons on macromolecules (49, 50), and/or through dipole-dipole interaction between water and macromolecule protons (58, 60-64).

In the first model the magnetization transfer (MT) is mediated by the exchangeable protons of OH, NH, and SH groups of the macromolecular phase which exchange rapidly with the bulk water. The exchangeable protons exchange
magnetization with the nonexchangeable protons of the macromolecules by cross-relaxation.

In the second model the MT involves hydration water molecules from the first layer of hydration which exchanges rapidly with the free bulk water. The hydration water molecules exchange magnetization with the protons of the macromolecules by cross-relaxation. It is restricted to rather few sites with relatively long-lived hydration water molecules. The presence of a surface hydroxyl and/or an amine group on the macromolecules is necessary for MT. However, the MT is not a result of the exchange of hydroxyl and amino protons, but to the exchange of hydration water molecules that are supposedly immobilized by the hydroxyl and amino groups.

Figure 1. The two models of MT between water and macromolecular matrix (i.e. proteins and lipids, which contain XH groups, where X = O, N or S).

The competition between these two models remains an active area of research. Deuterium substitution studies in tissue (126), protein solution studies with and without cross-linking agents and studies of dependence on the static field, pH, and temperature have shown the relative contribution of different physical mechanisms to MT between different proton pools (40, 76). However, the structural complexity of biological tissue makes it difficult to quantify the contributions of exchangeable protons versus hydration water to the total MT. Moreover, the mathematical formalism used to describe the MT effect applies in both models and cannot in itself distinguish between them.
2.3 Paramagnetic interaction

Paramagnetic compounds contain unpaired electrons. Unpaired electrons have magnetic dipoles, tending to align parallel to an external magnetic field. They have a relaxation mechanism approximately $657^2$ times more efficient than a proton. From the earliest work in NMR research, paramagnetic compounds have been demonstrated to have a dramatic effect on the relaxation times of protons in a solution. The idea of delivering paramagnetic agents into biological systems for 

\textit{in vivo} MRI was first proposed by Lauterbur et al. (71). The interactions between the unpaired electrons of a paramagnetic ion and the hydrogen nuclei of water molecules involve the two contributions of an inner and outer sphere (58, 72). The inner sphere contribution arises when a water molecule is associated with a solute long enough to form an identifiable chemical complex. The outer sphere is caused by fluctuations in the local magnetic field generated at the nucleus site by the electron’s magnetic moment as the water molecules diffuse close to the paramagnetic centers. A theoretical explanation for the inner sphere contribution is described by the Solomon-Bloembergen-Morgan (SBM) equations (9, 10). The theory for the outer sphere contribution incorporates the effects of fluctuations due to electronic relaxation as well as that due to translational diffusion. The derived expressions have some similarity with the SBM equations. The effectiveness of paramagnetic relaxation enhancement depends on many variables including the magnetic moment, electron-nuclear distance, field strength, and paramagnetic correlation time.

The longitudinal or transverse relaxivity ($r_{1,2}$) is the change in a relaxation rate per concentration of paramagnetic compound ($c$) as follows:

\[ r_{1,2} = \frac{\Delta T_{1,2}}{c} \]

where $\Delta T_{1,2}$ is the difference in the relaxation rates measured in the presence and absence of paramagnetic compound. The relaxivity describes the ability of each paramagnetic compound to catalyze relaxation of bulk water protons.

Paramagnetism arises from unpaired electron spins in either 3d (transition metal) or 4f (lanthanide) orbitals, a property shared by a significant number of metal ions. Paramagnetic compounds can enhance proton relaxation (relaxation agent), shift the resonance of a nearby nucleus (shift agent), and work as a magnetic susceptibility agent. Gd$^{3+}$ has seven unpaired electron spins coupled with relatively long electron spin relaxation times functioning primarily as a relaxation agent. Gd-metal is toxic, therefore it must be chelated, or surrounded by a ligand such as diethylenetriaminepenta-acetic acid (DTPA).
The addition of a paramagnetic compound causes an increase in the longitudinal and transverse relaxation rates $1/T_1 (R_1)$ and $1/T_2 (R_2)$, respectively, of the solvent nuclei. Increases in $R_1$ and $R_2$ result in a signal increase or decrease in MR imaging, respectively. However, in tissues the relative contribution of the Gd-DTPA compound is larger on $1/T_1$ than on $1/T_2$. Thus $T_1$-weighted imaging protocols, which minimize competing $T_2$ effects, are desirable.

3 Magnetization transfer

3.1 The theory of MT

MT imaging encompasses the family of techniques that generate image contrast of water containing macromolecular structures. The original experiments that exploited the saturation transfer method were performed in a system which was comprised of spin pools with clearly different chemical shifts (38, 80). In biological tissues the proton resonance of exchanging pools has nearly the same chemical shift. Therefore the saturation techniques are conducted in a way that differentiates the pools with respect to relaxation times instead of a chemical shift. In biological materials, MT or cross-relaxation is commonly modeled by two spin pools identified by their different $T_2$ relaxation times. The free water proton pool with a long $T_2$ gives rise to a narrow spectral line detected in imaging. The bound proton pool with very short $T_2$ gives rise to a broad spectral line which is not directly observed in MR imaging. In the MT technique RF pulses are used to selectively saturate protons in the bound pool (macromolecules). This saturation effect is transferred subsequently (by dipolar and chemical exchange interactions) to protons in free water, and is proportional to the relative sizes of the pool, individual proton relaxation rate, and cross-relaxation rate (see Fig. 2).

![Figure 2. Schematic diagram illustrating the two pools of protons.](image-url)
The widely adopted two pool model which is based on six coupled Bloch equations incorporating cross relaxation between mobile (A) and immobile (B) spins via dipole-dipole coupling. The model is modified to accommodate the non-Lorentzian line-shapes of immobile spins (48, 75, 92). The steady-state solution of the six equations can be given by

\[
\frac{M_s}{M_0} = \frac{R_A R_{BA} + R_A R_B + R_A R_{RFB} + R_B R_{AB}}{(R_A + R_{RFA} + R_{AB}) (R_B + R_{RFB} + R_{BA}) - R_{AB} R_{BA}} \tag{9}
\]

where

\[
R_{RFi} = \omega^2 \pi g_i (2\pi\Delta) \tag{10}
\]

where \(i\) indicates spin A or B. \(R_A\) and \(R_B\) are, respectively, the longitudinal relaxation rates of the A and B spins without cross-relaxation. \(R_{AB}\) and \(R_{BA}\), respectively, are the cross-relaxation rates from A spin to B spin and vice versa. \(R_{RFA}\) and \(R_{RFB}\) are the rates at which longitudinal magnetization is lost due to the direct effects of the off-resonance irradiation. \(\Delta\) is the offset frequency in Hz, \(\omega\) is angular frequency (rad/s). \(g_A (2\pi\Delta)\) is the Lorentzian line-shape for A spins. For immobile spins, \(g_B (2\pi\Delta)\) can be Gaussian (48) or super-Lorentzian (92) line-shapes. Recently, the use of flexible line-shapes for tissues has improved the agreement further (75).

In the case of complete saturation of the immobile spin pool and without the off-resonance effect on the mobile spin pool the steady state solution for the longitudinal magnetization of the mobile proton spin pool is

\[
\frac{M_s}{M_0} = \frac{R_A}{R_{AB} + R_A} \tag{11}
\]

and \(T_{1sat}\) can be given by

\[
T_{1sat} = \frac{1}{R_{AB} + R_A} \tag{12}
\]

Thus

\[
R_{AB} = \frac{(1 - \frac{M_s}{M_0})}{T_{1sat}} \quad \text{and} \quad R_A = \frac{M_s}{M_0} \frac{1}{T_{1sat}} \tag{13 (a, b)}
\]
The equation 11 has been originally described by Forsen et al. (38) for MT rate measurement. Equations 11 to 13 were the basis of MT contrast which was introduced by Wolf and Balaban (122) to be applied in MR imaging. In the case of incomplete saturation, apparent relaxation parameters such as apparent cross-relaxation rate $K_{app}$ can be defined. The $K_{app}$ becomes equivalent to $R_{AB}(K_f)$ when total saturation of the immobile spin pool is achieved (13).

3.2 MT techniques

The continuous wave (CW) technique employs an off-resonance pulse with a small amplitude and a long duration to continuously irradiate a sample at a frequency several kilohertz from the free water resonance (42, 105, 122). This causes saturation of the bound pool while leaving the free pool unaffected. The RF waveform can be rectangular or Gaussian. Because of specific absorption rate (SAR) constraints, CW methods are largely limited to low field systems.

Implementation of the MT technique at high fields has generally involved pulsed MR methods. These methods can be performed with either off-resonance or on-resonance pulses (41, 51, 52, 103, 104). In the on-resonance technique, a RF pulse is applied at the frequency of the free water resonance. If the total RF irradiation time is short compared to the $T_2$ of the free water and long compared to the $T_2$ of the bound protons, the result is a net rotation of the bound proton spins while the free spins have a net rotation of 0°. The off-resonance technique is similar to the continuous wave technique where the long saturation pulse is replaced by multiple, short duration, high intensity RF pulses.

3.3 Applications of MT in MRI

3.3.1 MT in vitro

Simple phantoms, such as agar gel or cross-linked protein (16, 58, 60, 61, 64), which reproduce many of the features of relaxation found in tissues, and biological samples such as cartilage (42), and white and gray matter (57, 65), were used in MT studies. MT imaging has been quantitatively investigated and modelled as a function of the amplitude, offset and duration of the off-resonance pulse (13, 48, 75, 93). These measurements give relaxation times of the immobile proton pool and the exchange rates between immobile and mobile proton pools. Moreover, Lee et al. (73) presented a practical method for estimating the MT immobile pool fraction ($M_{0b}$) and suggested that $M_{0b}$ is a more sensitive indicator of changes with disease and tissue type than MTR. In case of complete saturation of the macromolecular pool and no direct saturation of the
free water proton pool, simple measurements with and without MT pulses were used to calculate the MT ratio MTR or MTC (1-Ms/M0) and cross-relaxation rate (42, 61, 105, 118). The signal intensity ratios with complete and incomplete saturation of the macromolecules were also used to calculate the so-called MTR or MTC (1-I s/I0). The different measurement conditions makes the interpretation and comparison of the results difficult. Therefore, Berry et al. (7) suggested that the effective flip angle of the saturation pulse divided by the pulse repetition time can be used as a predictor of MTR. Phantom and simulated measurements have been used to study and optimize the imaging parameters (4, 34, 88). Finelli et al. (34) have developed an equation of brain tissue magnetization without and with a MT pulse, and have applied it for different flip angles. The degree of saturation in a two-spin system has been studied to find the experimental conditions which produce the maximal MT contrast (88).

3.3.2 MT in vivo

Since the first demonstration of MT images by Wolf and Balaban (122), MT images have been investigated as a means of producing a novel form of contrast on a MR image (4, 90, 124). Application of MT imaging can be divided into two main categories: contrast improvement and tissue characterization. Improvement in image contrast was observed in the heart and knee (3, 123), and in breast, liver and brain abnormalities (23, 54, 116). MT imaging has been used in MR angiography for improving the conspicuousness of blood vessels in the brain (43, 85).

Some investigators have demonstrated that MT parameters (Ms/M0 and cross-relaxation rate, or Is/I0) can be used in assessing grades of gliomas (69, 79), to evaluate cerebral hemorrhage (91) and Wallerian degeneration in the animal model (74), in characterizing demyelination (23, 24, 114), in differentiation of benign from malignant head and neck neoplasms (82, 125), in the differentiation of hepatic haemangiomas from metastases (46), to discriminate between neoplastic and normal breast tissue (17) and to evaluate diseases of muscle (86, 87).

3.3.3 MT and paramagnetic contrast agents

Gd-DTPA works by reducing the T1 and T2 of the lesion that it enters. When a low Gd-DTPA concentration is used, T1 shorting predominates, thereby resulting in a relative signal intensity increase in the lesion in T1-weighted images. Gd-DTPA enhancement is not significantly mediated by macromolecular interaction and is, therefore, not suppressed remarkably by MT pulses. Thus the MT effect of an enhanced lesion is reduced relative to that of non-enhanced tissue. The effect of MT and conventional sequence parameters were studied in a phantom simulating Gd-DTPA enhanced brain
lesions (33). Concurrent use of MT and the administration of a paramagnetic contrast agent (Gd-DTPA) has been shown to improve visualization of lesions in patients with stroke (32, 84), primary brain tumour (32, 66, 82, 89), brain metastases (32, 66, 89, 95), demyelinating disease, and inflammatory or infectious conditions (32, 89, 113). It has been reported that the contrast enhancement of a standard dose (0.1 mmol/kg) of Gd-DTPA combined with MT is equivalent to that which could be obtained using a triple dose (0.3 mmol/kg) of Gd-DTPA at 1.0 T (56) and at 1.5 T (32, 84). However, some investigators (35, 117) found that a triple dose Gd-DTPA is more effective than a single dose of Gd-DPA combined with MT at 1.5 T.

4 Spin lock

4.1 On- and off-resonance spin lock

The spin lock (SL) technique enables study of relaxation processes that are effective at very low field strengths while maintaining the high signal-to-noise ratio provided by the main magnetic field.

![Figure 3. On-resonance and off-resonance SL techniques.](image)

In an on-resonance SL technique, a RF pulse is applied at the Larmor frequency (Fig. 3 (a)) (110). The nuclear magnetization relaxes along the locking field (B_{1L}) during the locking period (T_L). The relaxation is characterized by the relaxation time T_{1ρ}, the spin-lattice relaxation time in the on-resonance rotating frame and it is in the case ω_0^2τ^2>>1 negligibly influenced by the much higher polarizing main magnetic
field \( (B_0) \) (77). This allows the study of tissue relaxation processes effective at low field strengths without any significant contribution from the main magnetic field. The specific absorption rate (SAR) is proportional to the product \( B_{1L}^2 B_0^{2} \text{TL/TR} \) (110). Thus, human on-resonance SL imaging at high field strengths is limited by heating of tissues.

In an off-resonance SL experiment, an RF pulse is applied at a specific amplitude \( (B_{1L}) \) and offset frequency \( (f_L) \) (Fig. 3 (b)) (102, 110). The locked nuclear magnetization relaxes along the direction of the effective field \( (B_{\text{eff}}) \) which rotates at angular frequency \( \omega_{\text{eff}} \). The relaxation is characterized by the relaxation time \( T_{1\rho}^{\text{off}} \), the spin-lattice relaxation time in the off-resonance rotating frame. \( B_{\text{eff}} \) is inclined to the static magnetic field \( (z\text{-axis}) \) at an angle \( \theta \). \( T_{1\rho}^{\text{off}} \) contains contributions from both \( T_{1\rho} \) and \( T_1 \). \( T_{1\rho}^{\text{off}} \) approaches \( T_1 \) as the frequency offset of \( B_{\text{eff}} \) increases i.e. as the direction of \( B_{\text{eff}} \) approaches the direction of \( B_0 \) and \( \theta \) approaches zero. When \( \theta \) becomes zero \( T_{1\rho}^{\text{off}} \) becomes equal to \( T_1 \). Correspondingly, \( T_{1\rho}^{\text{off}} \) approaches \( T_{1\rho} \) when the direction of \( B_{\text{eff}} \) approaches the xy-plane and \( \theta \) approaches 90°. As \( T_1 \) becomes larger with higher field strengths, the \( T_1 \) contribution to \( T_{1\rho}^{\text{off}} \) becomes smaller.

4.2 \( T_{1\rho} \) - and \( T_{1\rho}^{\text{off}} \)-relaxation and dispersion

The SL effect is a new parameter, which is a function of \( T_{1\rho} \) but more easily applied in clinical studies. Determination of the SL effect has been shown to be promising in characterization of liver lesions (46) and head and neck tumours (82). The single slice SL sequence has been used to calculate \( T_{1\rho} \)- and \( T_{1\rho}^{\text{off}} \)-relaxation parameters. It has also been used to characterize benign and malignant head and neck tissues (82). Recently, multiple slice 2D on- and off-resonance SL imaging techniques have been introduced (102, 111) and applied to liver tumour imaging (46). Multiple slice imaging may be useful when a large volume should be covered. The techniques allow the use of a short echo time which reduces motion artifacts.

The SL technique allows the study of field dependence i.e., dispersion of relaxation at a very low field range. The dispersion information is related to tissue-specific properties such as the size distribution of macromolecules and the concentration of paramagnetic substances (110).

\( T_{1\rho} \)-dispersion is the dependence of \( T_{1\rho} \) on the strength of the locking field \( B_{1L}. \) \( T_{1\rho} \)-dispersion has been studied in brain infarcts (108), multiple sclerosis (109), normal abdominal tissues (112), head and neck tumours (83), normal and diseased muscle (70, 120, 121), human breast tissues (101), normal and degraded bovine articular cartilage (25), mouse carcinoma (99), mouse embryos (30), mice tissues (20) and agarose gels (2). \( T_{1\rho} \)-dispersion was found to be useful in the distinction between benign and malignant head and neck tumours (83) and between normal and diseased muscle
tissue (70). $T_{1\rho}$-weighted images of normal and degraded cartilage have been suggested to reveal structure not found in conventional $T_1$ or $T_2$ weighted images (25). Engelhardt et al. (30) proposed the possibility of MR histology by using the $T_{1\rho}$ imaging technique. Rizi et al. (97) demonstrated the feasibility of proton $T_{1\rho}$-dispersion imaging for detection of intravenous $H_2^{17}O$ in a living mouse brain.

The Cole-Cole and similar functions have been successfully applied to $T_1$-dispersion of protein solutions and tissues (12, 36, 37, 58). Recently Hackmann et al. (44, 45) have derived an expression for $1/T_{1\rho}$ in a biological system which shows good agreement between theory and the experiment data. The $1/T_{1\rho}$ values for proteins were also fitted to a simple classical BPP type relaxation model to obtain $1/T_{1\rho}$ dispersion curves (119). They proposed that this model is not valid at very low $B_{1L}$ fields.

$T_{off_{1\rho}}$-dispersion is the dependence of $T_{off_{1\rho}}$ on the strength of the effective locking field ($B_{eff}$). $T_{off_{1\rho}}$-dispersion has been studied in mouse carcinoma (99). SL field cycling relaxometry has been developed to measure the dependence of $T_{off_{1\rho}}$ on the effective frequency (55). The steady state magnetization ($M_s/M_0$) and relaxation rates ($1/T_{off_{1\rho}}$) in the presence of an off-resonance RF irradiation has been shown to provide structural and dynamic information on molecules in solution (18, 19).

### 4.3 Spin lock and paramagnetic contrast agent

The SL technique combined with simultaneous use of paramagnetic contrast agents has been shown to improve tissue contrast in a few studies (21, 115). The increased myocardium-blood contrast in SL GRE images with contrast medium was found at 1.5 T (21). A near resonance SL pulse used in conjunction with gadolinium has shown potential to improve visualization of enhancing brain lesions (115). Rommel et al. (98, 99) have shown that the $T_{1\rho}$-dispersion imaging was sensitive to the presence of a paramagnetic substance ($MnTPPS_d$) in a mouse tumour.
AIMS OF THE PRESENT STUDY

The main purposes of the study were:

1. To investigate the combined effect of Gd-DTPA and MT in cross-linked BSA to evaluate and optimize MT irradiation and imaging parameters; to evaluate the usefulness of simultaneous use of MT imaging and Gd-DTPA administration in brain lesions and to study the possibility of replacing a triple dose of Gd-DTPA (0.3 mmol/kg) with a MT pulse and single dose of Gd-DTPA (0.1 mmol/kg) (I).

2. To determine the SL and MT relaxation parameters $T_{1\rho}, T_{\text{off}1\rho}$ and $M_0/M_0$, $T_{1\rho}$ and $T_{\text{off}1\rho}$ dispersion, $T_{\text{sat}}$ and $M_0/M_0$, for normal head, neck, and brain tissues in order to characterize the tissues. The relaxation parameters were evaluated to optimize the contrast of MR images (III, IV).

3. To investigate the combined effect of Gd-DTPA and on- and off-resonance SL in cross-linked BSA; to evaluate the usefulness of simultaneous use of on-resonance SL imaging and Gd-DTPA administration in brain tumours (II, V).
MATERIAL AND METHODS

1 Material

1.1 Phantom samples

Bovine serum albumin (BSA) powder, fraction V from plasma (Sigma Chem., St. Louis, MO; MW=66000) and gadolinium-diethylenetriaminepenta-acetate (Gd-DTPA) (Magnevist®, Schering AG, Berlin, Germany) and gelatin (Meira Oy, Helsinki, Finland) were used in studies I, II and V.

A phantom consisted of a container with 25 tubes (I) and 20 tubes (II, V). The tubes were filled with different concentrations of cross-linked BSA (2.5, 5, 10, 15, 20% of weight (I) and 5, 10, 15, 20% of weight (II, V)) and Gd-DTPA (0, 0.02, 0.05, 0.2, 0.5 mmol/l (I, II, V)).

1.2 Normal volunteers and patients

Ten patients, 7 males and 3 females, with enhancing brain tumours were included in study I. The patients were of ages 32 to 72 years.

Ten healthy volunteers between the ages of 25 and 44 years were included in study III.

In study IV there were sixty eight healthy volunteers, 38 males and 30 females, aged 21 to 50 years.

In study V, eleven patients with histologically verified gliomas, 8 males and 3 females, aged between 29 and 78 years, were studied.

2 Methods

All imaging was performed with a low field (0.1 T) resistive-magnet imager (Merit®, Picker Nordstar, Inc., Helsinki, Finland) using a head transmitting/receiving coil.

2.1 Conventional relaxation time measurements (T₁ and T₂)

In studies I, III, IV and V, spin-lattice relaxation time T₁ was measured using a standard inversion recovery (IR) sequence with field echo data collection, and the spin relaxation time T₂ was measured using a spin echo (SE) sequence.
2.2 Magnetization transfer technique

2.2.1 MT measurements

The MT measurements were performed by employing off-resonance irradiation combined with a conventional inversion recovery (I) or gradient echo (GRE) imaging sequence (IV).

In studies I (protein samples) and IV (volunteers) the MT parameters were measured with an amplitude ($B_s$) of 25 $\mu$T and a frequency offset ($F_s$) of 8 kHz, corresponding to $\theta \approx 8^\circ$.

The signal intensity of the MT- or SL-weighted sequence can be described by the following equation:

$$ S \propto A e^{-\frac{t}{T}} + B $$ (14)

In the IR sequence with MT, $M_0 = -(A+B)$, $M_s = B$ and $t = T_I$. In the GRE sequence with MT, $M_0 = A+B$, $M_s = B$ and $t = T_s$. In both the IR and GRE sequences $T = T_{1_{\text{sat}}}$. $M_s$ is the equilibrium magnetization of a mobile water proton with, and $M_0$ without the saturation of an immobile macromolecule proton. $T_{1_{\text{sat}}}$ is the observed relaxation time of a mobile water proton with the saturation of an immobile macromolecule proton and $T_s$ is the duration of the off-resonance irradiation.

2.2.2 MT imaging combined with Gd-DTPA

In study I, the MT effect of protein samples with and without the addition of Gd-DTPA were studied as a function of $B_s$ and $F_s$. $B_s$ was varied from 0 to 55 $\mu$T and $F_s$ was varied from 2 to 25 kHz. $T_s$ was fixed at 2000 ms. The corrected MT is the signal decrease due to MT alone. It is determined by subtracting the signal observed in the MT experiment from the signal calculated for direct saturation. The effect of TR and TE on CNR with and without MT irradiation, and with different Gd-DTPA concentrations were studied on protein samples. An equation describing the signal intensity of the MT-weighted GRE sequence was derived. Using simulations, the dependence of CNR on the imaging parameters was studied and compared with the measurements.

In study I, the $T_1$-weighted and proton density weighted sequences of patients with and without MT irradiation were imaged before and after two different intravenous doses of Gd-DTPA. The MT effect was measured with $B_s = 25$ $\mu$T and $F_s = 8$ kHz. $T_s$ was 70 ms for the $T_1$-weighted sequence and 600 ms for the proton density weighted sequence.
2.3 On and off-resonance spin lock techniques

2.3.1 $T_{1\rho}$ and $T_{\text{off1\rho}}$ measurements

In studies II-V, the SL sequence consisted of a GRE imaging sequence with the addition of an adiabatic locking pulse. The adiabatic pulse ensures that the magnetization is always phase locked along $B_{1L}$ (on-resonance SL) or along $B_{\text{eff}}$ (off-resonance SL) (102).

In study III, the $T_{1\rho}$ of normal head and neck tissues was determined with a $B_{1L}$ of 35 µT. In study IV, the $T_{1\rho}$ of normal brain tissues were determined with a $B_{1L}$ of 50, 100, 150, 200 and 250 µT. In study V, the $T_{1\rho}$ of protein samples were measured with a $B_{1L}$ of 100 µT. The tissue signal intensity was calculated according to Eq. 14, where $M_0 = A + B$ and $B = M_e \approx 0$, as $B_0 \gg B_{1L}$. $T = T_{1\rho}$ and $t = TL$. $M_e$ is the equilibrium magnetization during a locking pulse and $M_0$ is the equilibrium magnetization without a locking pulse.

In study IV, the $T_{\text{off1\rho}}$ of normal brain tissues was measured with an off-resonance SL pulse with $\theta$-angles of 15, 30, 45 and 60° and $B_{1L}$ of 50 µT. The tissue signal intensity was described by Eq. 14, where $M_0 = A + B$ and $B = M_e$, $T = T_{\text{off1\rho}}$ and $t = TL$.

In the GRE sequence, a phase spoiling technique was used to destroy the transverse steady state signal. Thus, the transverse magnetization is spoiled prior to every RF pulse so that only the longitudinal magnetization attains a steady state. The determinations of the SL ($T_{1\rho}$, $T_{\text{off1\rho}}$, $M_e$) and the MT ($T_{1\text{sat}}$, $M_s$) parameters were performed by using single slice acquisition since the multislice on and off-resonance pulses are nonselective and their saturation effects are cumulative throughout the repetition time (111).

2.3.2 $T_{1\rho}$- and $T_{\text{off1\rho}}$-dispersion measurements

In study IV, for simplicity, an equation based on the assumption of a weak-collision, an effective correlation time, and with no exchange between the different pools was used. The equation is assumed to be valid for a low field in the rotating frame when $\tau \ll T_2$ (53). The $1/T_{1\rho}$ dispersions for the white and gray matters were fitted to the equation (2):

$$\frac{1}{T_{1\rho}} = \frac{1}{T_2} - A \left( \frac{1}{1 + 4 \omega_t^2 \tau^2} \right) + A$$

(15)
where $\tau$ is the effective proton correlation time for the slowest motion, $\omega_1$ is the angular frequency of the locking field and $A$ is the contribution of the protons with short correlation times (i.e. $\omega_1^2\tau^2 << 1$) to the observed relaxation rate.

The dependence of $T_{1\rho}$ relaxation times on $\theta$ were fitted according to the theoretical equation derived by Jones (53).

2.3.3 SL imaging combined with Gd-DTPA

In study II, in protein samples, on and off-resonance SL images were acquired with a $B_{1L}$ of 25 $\mu$T. For all off-resonance SL experiments $\theta$ values of 8, 15, 25, 35 and 45° were used. The relationship of the SL effect with protein and Gd-DTPA concentrations, and the effect of imaging parameters on the CNR were evaluated.

In study V, in protein samples, a $T_1$-weighted three dimensional (3D) GRE sequence with the addition of an on-resonance SL pulse was used to study the relationship between the measured SL effect ($S_{\text{Leff}}$) and the duration of the locking pulse without and with the addition of Gd-DTPA. TL values of 20, 40 and 57 ms and $B_{1L}$ of 100 $\mu$T were used.
RESULTS

This section reviews the main findings of the study. The original communications I-V are referred to for further details.

1 Magnetization transfer

1.1 MT of protein samples

In study I, the relaxation rates $1/T_1$, $1/T_2$ and $1/T_{1\text{sat}}$ of cross-linked BSA increased as the Gd-DTPA concentration (0.02-0.5 mmol/l) or the concentration of protein (5-20%) increased. The ranges of $T_2/T_1$ for 20, 15, 10, and 5% cross-linked BSA without Gd-DTPA to that with 0.5 mmol/l Gd-DTPA were 0.26-0.42, 0.26-0.52, 0.29-0.57 and 0.33-0.68. The $I_s/I_0$ and $M_s/M_0$ ratios increased with a decreasing protein concentration and with an increasing Gd-DTPA concentration. The $I_s/I_0$ ratio increased with an increased offset frequency and a decreased amplitude.

The combination of an offset frequency of 8 kHz and an amplitude of 25 $\mu$T produced close to the maximal MT effect (corrected) for protein samples with and without different Gd-DTPA concentrations as demonstrated in Fig 4 (reproduced data). The simulated and measured results for protein samples showed that the CNR with Gd-DTPA and MT was higher than the CNR with Gd-DTPA without MT. The optimal TR depends on both the protein and Gd-DTPA concentration. A TR of 125 ms gave a maximal CNR over a wide range of different BSA and Gd-DTPA concentrations. The maximal CNR for a $T_1$-weighted image can be obtained with the largest allowed $T_s$ whereas for a proton density image, the CNR reached maximum at $T_s$ values depending on the concentration of protein.

![Figure 4](image)

Figure 4. Corrected MT effect (the difference between the measured MT effect and the direct effect) for 20% cross-linked BSA without (a) and with 0.2 mmol/l Gd-DTPA as a function of $F_s$. The GRE 4500/15 sequence was used with $B_s$ of 10, 25, and 40 $\mu$T and $T_s$ of 2000 ms.
1.2 MT of patients and volunteers

In study I, in brain tumour patients there was a significant improvement in CNR on T1-weighted and proton-density-weighted images caused by MT irradiation after the standard dose of 0.1 mmol/kg of Gd-DTPA and after the cumulative dose of 0.3 mmol/kg of Gd-DTPA. The CNR after a triple dose of Gd-DTPA with conventional imaging was significantly better than that after 0.1 mmol/kg combined with MT imaging in the T1-weighted sequence.

In study IV, in volunteers, T1sat values were significantly shorter in the normal frontal white matter than in gray matter. No statistically significant differences were detected in the M0/M0 values between different brain regions.

2 Spin lock

2.1 T1ρ and Toff1ρ values of volunteers

In study III, T1ρ values of muscle and tongue were similar to but shorter than those of parotid gland and lymphatic tissues with a B1L of 35 µT. In study IV, the T1ρ values were significantly shorter for the frontal white matter than for the parietal white matter, with all B1L values in the range 50 µT to 250 µT. T1ρ values for the frontal white matter were significantly shorter than the T1ρ for the gray matter with all five different B1L values.

In study IV, with θ angles ranging from 60° to 15°, the Toff1ρ values showed statistically significant differences between the frontal white and gray matter, and between the parietal white and the gray matter. With θ angles of 30°, 45°, and 60°, the Toff1ρ values were significantly shorter in the frontal white matter than in the parietal white matter.

2.2 T1ρ- and Toff1ρ-dispersion values

In study IV, T1ρ for the white and gray matter increased significantly with increasing angular frequency ω1 (Fig 5). In study III, a large dispersion effect was detected in muscle and tongue, while intermediate values were found in lymphatic and parotid gland tissues.

In study IV, Toff1ρ of frontal white and gray matter (Fig. 5), and of parietal white matter decreased significantly with increasing θ, corresponding to decreasing the effective angular frequency ωeff. With decreasing θ, the difference in Toff1ρ values between the parietal white matter and gray matter increased. With increasing θ, the
difference in $T_{\text{off}}^{1 \rho}$ between the parietal and frontal white matter increased. For comparison, MT values for frontal white and gray matter are presented in Fig. 5.

Figure 5. $1/T_1^{1 \rho}$ (on-SL) and $1/T_{\text{off}}^{1 \rho}$ (off-SL) as a function of angular and effective angular frequency $\omega_1$ and $\omega_{\text{eff}}$, respectively, for (a) frontal white matter and (b) gray matter. $1/T_{1 \text{sat}}$ (MT) is also shown in the figure. $1/T_1^{1 \rho}$ was measured for $B_{1L}$ of 50, 100, 150, 200, and 250 $\mu$T. $1/T_{\text{off}}^{1 \rho}$ was measured for $\theta$ of 15, 30, 45, and 60° and $B_{1L}$ of 50 $\mu$T.

2.3 SL imaging combined with Gd-DTPA

In studies II and V, the SL pulse duration had a significant influence on the measured $S_{\text{LEff}}$ at all protein concentrations. The $S_{\text{Eff}}$ was strongly dependent on the protein concentration (5-20%). In $T_1$-weighted images of a protein sample, increasing the Gd-DTPA concentration decreased the off-resonance $S_{\text{eff}}$ when using small $\theta$ values, but did not have a significant effect on the off-resonance $S_{\text{eff}}$ with large $\theta$ values and on-resonance $S_{\text{eff}}$. On proton density-weighted images, $S_{\text{eff}}$ differed at different Gd-DTPA concentrations, at different $\theta$ values (8, 15, 25, 35, and 45°). The CNR was depended on TR and $\theta$. The optimal CNR was obtained with a small TR and with a $\theta$ angle of 8°.

In study V, on the pre-contrast and post-contrast images, $S_{\text{eff}}$ in the tumour was significantly smaller than in the normal white matter and thalamus. The injection of a contrast medium did not have a significant effect on the measured $S_{\text{eff}}$ either in the enhancing tumours or in the non-enhancing white matter or thalamus areas.
DISCUSSION

1 Magnetization transfer

1.1 MT parameters (M₀/M₀, K_app, T₁sat)

The MT phenomenon is complex due to the many parameters that are involved, especially under conditions of incomplete saturation (see Eq. 9). When the saturation of the restricted mobility spin pool is incomplete apparent M₀/M₀ and K_app are dependent upon the amplitude and offset frequency of the saturation pulse (11). For determining MT parameters (T₁sat and M₀/M₀) in studies I and IV measurements were performed under conditions close to complete saturation to reduce the effect of several parameters (Eq. 9) and to approach the M₀/M₀ and K₀ values.

In study IV, M₀/M₀ values did not differ significantly in the different normal brain matter regions. Moreover, in study I, M₀/M₀ ratios for 5, 10, 15, and 20% cross-linked bovine serum albumin concentrations were similar, which indicates lack of dependence of M₀/M₀ on macromolecule concentration in cross-linked BSA. The results are in agreement with the studies of Kurki et al. (67) and Morrison et al. (93) which reported a similar M₀/M₀ ratio for white and gray matter. Beaulieu et al. (5) found that M₀/M₀ varies little between myelinated and non-myelinated garfish nerves and concluded that M₀/M₀ is not sensitive to myelin. Gray et al. (42) showed that M₀/M₀ is not very sensitive to cartilage collagen concentration in the physiological range. Scholz et al. (105) reported that M₀/M₀ did not vary much in control and hypertensive rat tissue in vitro. These results are in agreement with Eq. 13, which shows that the M₀/M₀ = R_A T₁sat. In study I, both relaxation rates (R_A, 1/T₁sat) increase linearly with protein concentration so that the product R_A T₁sat remains nearly constant and M₀/M₀ thus insensitive to macromolecular or water concentration. Moreover, according to Eq. 11 M₀/M₀ contains contributions from the hydrodynamic effect and the cross-relaxation effect. Does et al. (22) reported that the myelinic nerve component may possess a higher R_A than the axonal component but the two components have a similar product of R_AB and T₁ and thus similar MTR (1- M₀/M₀). They suggested that instead of measuring MTR at a steady-state, measuring MT with a relatively short pulse (truncated MT (94)), would result in a transient MTR which is more dependent on the myelinic MT component. The transient MT measurement with a T₁-weighted sequence has often been used in clinical MT studies. Many of these studies suggested that the reduction in signal intensity (1- I₀/I₀), which they called the MT effect, is tissue specific. However, performing the measurements under incomplete saturation makes the interpretation and comparison of results difficult.
In the study I, both $T_{1\text{sat}}$ and $K_{\text{app}}$ showed clear dependence on the protein concentration and brain tissue type so that they are more tissue specific parameters than $M_r/M_0$. Scholz et al. (105) also found significant correlations between tissue water content and $T_1$, $T_2$, $T_{1\text{sat}}$ and $K_{\text{app}}$ and showed that $T_{1\text{sat}}$ and $K_{\text{app}}$ were different between the control and hypertensive rats. Kurki et al. (69) showed that the cross-relaxation rate revealed more significant differences among tumour groups than MTR ($1 - M_r/M_0$) measurements. The cross-relaxation rate has been shown to depend on the surface chemistry, concentration and dynamics of the macromolecules (16, 105). The results agree with the work of Eng et al. (29), which demonstrated that the constructed $K_{\text{app}}$ maps of the rabbit kidney, in vivo, have greater contrast than $M_r/M_0$ images. Koenig et al. (61) also suggested that cross-relaxation rate values can be used to differentiate between tissues.

In study I, the cross-relaxation contribution of the cross-linked BSA to $1/T_1$ was about 20%. In study IV, the cross-relaxation contribution of the frontal and parietal white and gray matter to $1/T_1$ were about 34%, 30%, and 17%, respectively. This agrees with the studies of Koenig et al. (58) and Zhong et al. (126) which showed comparable contributions to $1/T_1$ from hydrodynamic and cross-relaxation mechanisms at a low field, and that the cross-relaxation contribution decreased with increasing main field strength. Moreover, it has been suggested that at a very low field strength the cross-relaxation mechanism is the main source of relaxation (14).

1.2 Optimization of conventional and MT measurement parameters

The optimization of the irradiation parameters to maximize MT is important. The maximal MT effect can be provided with maximal indirect saturation and minimal direct saturation. Kucharczyk et al. (65) reported that the maximal MT effect of white matter lipids occurs with a pulse amplitude of approximately 16 $\mu$T and at an offset frequency of about 7.5 kHz at 1.5 T. Our result (study I) showed that in protein samples the combination of an amplitude of 25 $\mu$T and offset frequency of 8 kHz produced a close to maximal MT effect for protein samples without and with different Gd-DTPA concentrations. However, it seems that the offset frequency and amplitude at which maximal MT occurs varied with tissue type (93).

To evaluate and optimize the imaging parameters an equation was derived for the signal intensity of MT-weighted GRE sequence (Eq. 2, study I). The equation can be used to study the effect of the TR, TE, flip angle and MT pulse duration. Our study demonstrated the importance of the choice of TR in post-contrast imaging without and with MT imaging. The post-contrast CNR without MT imaging is more dependent on TR than with MT imaging. Thus, an improper choice of TR may lead to incomplete conclusions when comparing the importance of MT and Gd-DTPA dose for the CNR.
Moreover, CNR also depends on the flip angle and the field strength. The maximal CNR with Gd-DTPA and MT was observed with a small TR. However, a significant improvement in CNR due to MT was obtained with a large TR, where there was no contrast medium enhancement without MT (Fig. 4, study I).

1.3 Combined effect of Gd-DTPA and MT

Contrast enhancement in MR imaging is due to a direct water-gadolinium ion interaction, not macromolecular cross-relaxation. MT pulses therefore preferentially suppress the signal from background tissues and render the gadolinium enhanced area more conspicuous. In our protein samples (study I), the addition of Gd-DTPA increased the relaxation rate $R_A (1/T_1)$ and $1/T_2$ by the same amount, the $T_1$ relaxivity of Gd-DTPA was close to the $T_2$ relaxivity for all protein concentrations. However, due to the smaller original value, $T_2$ is not affected by the Gd-DTPA as much as $T_1$. Thus the overall effect of Gd-DTPA is to increase $T_2/T_1$. Increasing $R_A$ by the addition of Gd-DTPA increased the $M_s/M_0$ and $I/I_0$ ratio (see Eq. 11). Beritini et al. (6) have suggested that contrast agents which increase $R_A$ and $1/T_2$ by the same amount, and thus increase $T_2/T_1$, are those useful in MT experiment.

According to our study $M_s/M_0$ values seem to become more sensitive to protein concentration after the addition of Gd-DTPA. Similar observations have been seen in vivo, where structures normally enhancing with Gd-DTPA (e.g., choroid plexus, dural sinuses, pituitary, pineal) are more conspicuous when MT pulses are used (28).

In patient studies (I) after a standard and a cumulative triple dose the MT effect in the enhancing lesions was smaller than in normal white matter on $T_1$-weighted and on proton density-weighted images. The use of MT irradiation improved the tumour CNR after both contrast agent doses on $T_1$-weighted and proton density-weighted images. However, the results indicate that MT imaging combined with a single dose of Gd-DTPA cannot replace the imaging with a triple dose of Gd-DTPA at 0.1 T. A similar finding has been reported by Fisher et al. (35) and van Waesberghe et al. (117), but some investigators reported that triple dose Gd-DTPA may be replaceable with MT imaging combined with single dose Gd-DTPA (32, 56, 84). The differences in the results may be related to the selected parameters, especially TR, MT parameters, and the different field strengths used. We can conclude that MT imaging at imaging fields with clinical Gd-DTPA concentrations improves contrast. The contrast improvement is due to the difference in the efficiency of MT in non-enhancing, macromolecule-rich tissue and in enhancing tissue.
2 Spin lock

2.1 $T_{1\rho}$ and $T_{\text{off}1\rho}$ relaxation and dispersion values

$T_{1\rho}$-dispersion and $T_{\text{off}1\rho}$-dispersion are additional contrast parameters for MR imaging. Previously, it has been observed that protein rich tissues, such as muscle and liver, have a considerable $T_{1\rho}$-dispersion with a $B_{1L}$ range of 35 to 500 $\mu$T. The $T_{1\rho}$-dispersion effect was found to be useful in the distinction between benign and malignant head and neck tumours (83), and between normal and diseased muscle tissue (70). Fresh brain infarctions and plaques of multiple sclerosis have a long $T_{1\rho}$ and a slightly smaller $T_{1\rho}$-dispersion than normal brain tissue in the $B_{1L}$ range 50-460 $\mu$T. Duvvuri et al. (25) demonstrated significant $T_{1\rho}$-dispersion in normal bovine articular cartilage in the $B_{1L}$ range 2-211 $\mu$T. According to our results brain tissues showed a considerable dispersion in the $B_{1L}$ range of 50 to 250 $\mu$T (study IV) and head and neck tissues in the $B_{1L}$ range of 35 to 100 $\mu$T (study III). However, the $T_{1\rho}$-dispersion in the $B_{1L}$ range 50–250 $\mu$T of different normal brain regions were similar and thus not useful in normal brain matter discrimination.

The measured $1/T_{1\rho}$ values of brain tissues were fitted to Eq. 15 to determine the parameter $A$ and the effective correlation time $\tau$. The parameter $A$ was proportional to water concentration. $\tau$ was insensitive to the type of brain tissue. The BPP-type model applied in Eq. 15 is used to examine molecular motions in homogeneous liquids. In the case of tissues where two or three different interacting proton pools exist, Eq. 15 is not necessarily appropriate. However, using this equation it may be possible to approximate the effective correlation time for white and gray matter. Virta et al (119) also demonstrated that $\tau$ was insensitive to protein concentration. The insensitivity of $\tau$ may be explained by the fact that the observed $T_{1\rho}$-dispersion is not related to a correlation time as has been suggested by Brown III and Koenig (14).

$T_{\text{off}1\rho}$-dispersion study can be performed by changing the $B_{1L}$ or frequency offset. In study IV the $T_{\text{off}1\rho}$-dispersion was performed by changing the offset frequency keeping the $B_{1L}$ constant so that the angle $\theta$ between $B_{\text{eff}}$ and the $z$-axis will change. Angle $\theta$ had a significant effect on the off-resonance relaxation parameters and thus on the sensitivity of the method. By increasing $\theta$ the difference in $T_{\text{off}1\rho}$ between the parietal and frontal white matter increased. By decreasing $\theta$, the differentiation between the parietal white and gray matter increased. Thus $T_{\text{off}1\rho}$-dispersion information of different brain regions were useful in normal brain matter discrimination. The measured $T_{\text{off}1\rho}$ values of brain tissues were fitted to the equation derived by Jones (53). $\tau$ was similar in the different types of normal brain tissue as in on-resonance experiments.
2.2 Combined effect of Gd-DTPA and spin lock

The addition of Gd-DTPA to protein samples reduces relaxation times $T_1$, $T_{1p}$ and $T_{1eff}$. On proton density-weighted images (study II), increasing Gd-DTPA concentration had a significant effect on on- and off-resonance $S_{Leff}$. On $T_1$-weighted images (study II), increasing Gd-DTPA concentration decreased the off-resonance $S_{Leff}$ when using small $\theta$ values, but did not have a significant effect on off-resonance $S_{Leff}$ with large $\theta$ values and on-resonance $S_{Leff}$.

In patient studies (V) the injection of contrast medium did not significantly alter the measured on-resonance $S_{Leff}$ in the enhancing tumours. There are two main reasons. The first is that the absolute increases of relaxation rates $1/T_1$ and $1/T_{1p}$ due to Gd-DTPA are about the same (see Fig. 2, study V). However, due to the smaller original value, $T_{1p}$ is not affected by the Gd-DTPA as much as $T_1$. The second reason is that in the SL effect of our $T_1$-weighted sequence, the Gd-DTPA induced decrease of $T_{1p}$ was nearly compensated by the more significant Gd-DTPA induced decrease of $T_1$, as seen from Eq. 2 (study V).

In study II, the result indicates that the selection of angle $\theta$ and TR is important for improving the CNR when combined with the use of Gd-DTPA and off-resonance SL imaging. The best CNR after the addition of Gd-DTPA was obtained in $T_1$-weighted images with small $\theta$. However, Ulmer et al (115) showed that the maximal contrast between the enhancing lesion and normal brain was obtained using $T_1$-weighted imaging with an off-resonance pulse of amplitude $9.5 \, \mu T$ and an offset frequency of 300 Hz.

3 Comparision between conventional, MT and SL parameters

3.1 Comparison between MT and $T_2$

Many studies have found that in MTC-complemented $T_2$-weighted images, the tissues that remained bright in long TE sequences (except fat) were also those that did not have large MT effects and remained bright in MTC enhanced images (4, 39, 122). Gochberg et al. (40) found that $1/T_2$ and $K_{app}$ have roughly similar dependencies on chemical composition and pH. Harrison et al. (47) suggested that the MT effect in normal muscle is closely correlated to intensity decrease in $T_2$-weighted images. Kurki et al. (68) found that the capability of the MT method in tumour characterization resembled that of $T_2$ contrast, but the MT method separated low grade gliomas, craniopharyngiomas and hemangioblastomas from other tumours better than $T_2$-weighted images. The observed similarity between MTC and $T_2$ is likely due to the fact that $T_2$ and MT are dependent on the concentration and mobility and structure of macromolecules. Moreover, this
similarity can be attributed to the suggested high contribution of MT to $T_2$ relaxation (62). In our study I, correlations between $1/T_{1\text{sat}}$ and $1/T_2$ and between $K_{\text{app}}$ and $1/T_2$ at different protein concentrations (without and with Gd-DTPA) were observed ($r^2 = 0.79$ and 0.74, respectively). In our study IV, the $T_2$ value was significantly shorter in the frontal white matter than in the parietal white matter, but the $T_{1\text{sat}}$ value was not. Harrison et al. (47) also suggested that MT can yield contrast in white matter that differs from that in $T_2$-weighting.

3.2 Comparison between SL and $T_2$

The image contrast on SL images has been shown to resemble that of $T_2$-weighted images. This is supported by a strong correlation between $1/T_1^\rho$ and $1/T_2$ ($r^2 = 0.995$) in different protein concentrations (without and with Gd-DTPA) (study V, Fig. 3). However, $T_1^\rho$ of various protein concentrations was systematically about 10% larger than $T_2$. In study IV, the ability of $T_1^\rho$ to differentiate between the frontal and the parietal white matter, and between the frontal white and the gray matter was close to that of $T_2$. In study III $T_1^\rho$ values at a $B_{1\text{L}}$ of 35 μT for head and neck were also close to $T_2$ values. Virta et al. (120) showed that $T_1^\rho$ is as sensitive as $T_2$ to the composition of muscle, whereas $T_1$ is less sensitive. They conclude that $T_1^\rho$ and $T_2$ provide relatively similar tissue contrast. Ulmer et al. (115) also reported that spin-density weighted images with an off-resonance saturation pulse of 14 μT and offset frequency of 300 Hz (near resonance) showed tissue contrast similar to $T_2$-weighted images. These results indicate that $1/T_1^\rho$ and $1/T_2$ relaxation rates are related. In $T_2$-weighted imaging, the long TE allows the spins to dephase which can cause image artifacts. In $T_1^\rho$-weighted imaging the spins are locked which together with the ability to use short TE reduces the movement and susceptibility artifacts compared to $T_2$-weighted imaging. Hence, SL imaging with a low $B_{1\text{L}}$ strength offers an alternative to $T_2$-weighted imaging.

3.3 Comparison between MT, on-resonance SL and off-resonance SL techniques and parameters

Both MT and SL imaging are generated by using a preparation pulse followed by a conventional imaging sequence. The differences between the MT, on-resonance SL and off-resonance SL techniques are related to the technique of performing the experiment. In the MT technique the RF pulse is employed to selectively saturate the bound protons of tissue while leaving the mobile tissue water protons unaffected. In off-resonance SL, the RF pulse is applied much closer to resonance than the MT pulse. Thus off-resonance SL saturates bound protons and in some degree directly the mobile water protons. In the on-resonance SL there is saturation of mobile and bound tissue-water protons. The off-
resonance SL technique has been used at a high field strength, instead of on-resonance SL, to reduce tissue heating. In the on-resonance SL experiments of study IV with $B_{1L}$ similar to the $B_{\text{eff}}$ of the off-resonance experiments the relaxation rates were different and the comparison between on and off-resonance SL is not straight forward. The angle $\theta$ is a measure of the amount of SL provided by an off-resonance RF pulse (102). When ($15^\circ \leq \theta < 90^\circ$) the relaxation behaves according to $T^{\text{off}}_{1P}$, $T^{\text{off}}_{1P}$ and $M_d/M_0$ increase with decreasing $\theta$ and approach MT parameters ($T_{1\text{sat}}, M_d/M_0$) when $\theta \leq 15^\circ$. For a pulse very far from resonance ($\theta \approx 0^\circ$) the relaxation approaches $T_1$ and when the pulse is on resonance ($\theta = 90^\circ$) the relaxation behaviour is described by $T_{1P}$.

It has been suggested that MT plays a dominant role in the relaxation observed with the SL-technique in protein-rich tissues (14). This suggestion was supported by Markkola et al. (82) who found a strong correlation between on-resonance SL and MT effects (82) and a strong correlation between $T_{1P}$-dispersion and MT effects (83) in head and neck tumours. However, Markkola et al. (82) also found that fat tissue and MnCl$_2$ solution showed no MT effects, whereas their SL effect was moderate. In our studies I and II the combined effect of Gd-DTPA and off-resonance SL imaging with small $\theta$ values is very similar to the combined effect of Gd-DTPA and MT imaging. In our study IV, the capabilities of $T^{\text{off}}_{1P}$, $T_{1P}$ and $T_{1\text{sat}}$ in separating frontal white matter from gray matter were similar. Moreover, $T_{1P}$ and $T^{\text{off}}_{1P}$ with angle $\theta$ at 30, 45, and 60° were able to separate frontal white matter from parietal white matter, but $T_{1\text{sat}}$ and $T^{\text{off}}_{1P}$ with $\theta$ at 15° were not.
CONCLUSIONS

1. Phantom studies demonstrated the importance of the choice of TR in the post-contrast sequence without and with a MT pulse. The post-contrast CNR without MT imaging is more dependent on TR than it is with MT imaging. Thus inappropriate choice of TR may lead to incomplete conclusions when comparing the importance of MT and Gd-DTPA dose for CNR. The maximal CNR with Gd-DTPA and MT was observed with a small TR. However, a significant improvement in CNR using MT was obtained with a large TR, where there was no contrast medium enhancement without MT. MT improved the CNR of brain lesions after single and triple Gd-DTPA doses on T1-weighted and also on proton density images. The results indicate that a single dose of Gd-DTPA combined with T1-weighted MT cannot, however, replace imaging with a triple dose. The best CNR was achieved when T1-weighted MT imaging was combined with a triple Gd-DTPA dose.

2. SL and MT parameters provide additional information and improve tissue discrimination. The $T_{1p}$, $T_{off}^{1p}$ and $T_{1sat}$ were statistically significantly shorter in the frontal white matter than in the gray matter. $T_{1p}$ and $T_{off}^{1p}$ with $\theta \geq 30^\circ$ were statistically significantly shorter in frontal than in parietal white matter. With angle $\theta$ ranging from 15° to 60° the values of $T_{off}^{1p}$ were statistically significantly shorter in parietal white matter than in gray matter. The $T_{1p}$ of white and gray matter increased significantly with increasing locking field amplitude. In head and neck tissues a considerable $T_{1p}$ dispersion was found in muscle, tongue, lymphatic and parotid gland. The $T_{off}^{1p}$ of white and gray matter decreased significantly with increasing $\theta$. $T_{off}^{1p}$ dispersion information of different brain regions was useful in normal brain matter discrimination while $T_{1p}$ dispersion was not. The duration, amplitude and $\theta$ of the MT pulse and SL pulse provide additional parameters for optimizing contrast in brain MT and SL imaging.

3. Off-resonance SL measurements of protein samples showed that the improvement in CNR after the addition of Gd-DTPA was dependent on angle $\theta$. The best CNR was obtained with small $\theta$ (8°). 3D on-resonance SL imaging with the addition of Gd-DTPA can be used in vivo to increase contrast of human gliomas. 3D $T_1$-weighted SL imaging showed a consistently smaller $SL_{eff}$ in the gliomas than in normal brain tissue. This indicates that SL imaging may be used for tissue characterization if the imaging parameters are optimized.
SUMMARY

A phantom containing different cross-linked bovine serum albumin and Gd-DTPA concentrations is an appropriate model for conventional, MT ($T_{1\text{sat}}$, $M_s/M_0$) and SL ($T_{1\rho}$, $T_{\text{off}_{1\rho}}$, $M_s/M_0$) parameters in normal or tumour tissue. The phantom work showed that the conventional imaging parameters (e.g., TR, TE) and the properties of the preparation pulses in MT imaging ($B_s$, $F_s$, $T_s$) should be optimized for each clinical application. The results demonstrated that the combination of an $F_s$ of 8 kHz and a $B_s$ of 25 µT produced a close to maximal MT effect for various protein concentrations, without and with different Gd-DTPA concentrations, at 0.1 T. A TR of 125 ms gave a maximal CNR over a wide range of different BSA and Gd-DTPA concentrations.

MT improved the CNR after single and triple Gd-DTPA doses on $T_1$-weighted and also proton density images. The best CNR was achieved when $T_1$-weighted MT imaging was combined with a triple Gd-DTPA dose. The clinical results indicate that a single dose of Gd-DTPA combined with MT cannot, however, replace imaging with a triple dose.

Theoretical and experimental dependence of $T_{1\rho}$ and $T_{\text{off}_{1\rho}}$ for brain tissues is presented and the interplay of $T_{1\rho}$, $T_{\text{off}_{1\rho}}$ and MT weighted contrast has been demonstrated. The duration, amplitude and inclination angle $\theta$, of the locking pulse provide additional parameters to optimize contrast in brain SL imaging. Both white and gray matter demonstrated considerable $T_{1\rho}$ dispersion in the $B_{1L}$ range from 50 µT to 250 µT, with a significant increase in $T_{1\rho}$ values as the $B_{1L}$ increased. However, $T_{1\rho}$ dispersion was similar for different normal brain regions. Thus, the $T_{1\rho}$-dispersion is unlikely to be useful in normal brain matter discrimination. The difference in $T_{\text{off}_{1\rho}}$ between parietal and frontal white matter increased by increasing $\theta$. With decreasing $\theta$, the differentiation between parietal white and gray matter increased. With the proton density imaging sequence the best contrast between white and gray matter was achieved with $\theta$ values from 15° to 45°. By keeping the $\theta$ constant (15°), the best contrast was obtained with short locking pulse durations.

The phantom work with the off-resonance SL technique showed that the improvement in CNR after the addition of Gd-DTPA was dependent on angle $\theta$. The best CNR was obtained with a small $\theta$ (8°). When applying the simultaneous use of Gd-DTPA and off-resonance SL imaging for protein samples using a relatively small $\theta$ angle, the measured $S_{\text{Leff}}$ decreased with increasing Gd-DTPA concentration. Thus the combined effect of Gd-DTPA and off-resonance SL imaging with small $\theta$ values was very similar to the combined effect of Gd-DTPA and MT imaging.

A strong correlation was observed between $1/T_{1\rho}$ and $1/T_2$ in different protein concentrations (without and with Gd-DTPA). However, the $T_{1\rho}$ of various protein concentrations was systematically larger than $T_2$. The correlation indicates that
$1/T_1$ and $1/T_2$ relaxation rates are related. Hence, the SL imaging with $T_2$-like contrast also offers an alternative to $T_2$-weighted imaging.

The usefulness of 3D SL imaging in increasing contrast in the MRI of human gliomas has been demonstrated. The results of 3D $T_1$-weighted SL imaging showed a consistently smaller $SL_{\text{eff}}$ in gliomas than in normal brain tissue, which indicates that SL imaging may be used for tissue characterization if the imaging parameters are optimized.
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REFERENCES


74. Lexa FJ, Grossman RI, Rosenquist AC. Dyke Award paper. MR of wallerian
degeneration in the feline visual system: characterization by magnetization transfer

75. Li JG, Graham SJ, Henkelman RM. A flexible MT line shape derived from tissue

76. Liepinsh E, Otting G. Proton exchange rates from amino acid side chains

77. Look DC, Lowe IJ. Nuclear magnetic dipole-dipole relaxation along the static and
(1966).

78. Lundbom N, Brown III RD, Koenig SH, Lansen TA, Valsamis MP, Kasoff SS.
Magnetic field dependence of $1/T_1$ of human brain tumours: correlations with

79. Lundbom N. Determination of magnetization transfer contrast in tissue: an MR

80. Mann BE. The application of the Forsen-Hoffman spin-saturation method of
measuring rates of exchange to the $^{13}$C NMR spectrum of N, N-


82. Markkola AT, Aronen HJ, Paavonen T, Hopsu E, Sipilä LM, Tanttu, JI, Sepponen
RE. Spin lock and magnetization transfer imaging of head and neck tumours.

83. Markkola AT, Aronen HJ, Paavonen T, Hopsu E, Sipilä LM, Tanttu JI, Sepponen
RE. $T_1$ dispersion imaging of head and neck tumours: A comparison to spin lock
and magnetization transfer techniques. J. Magn. Reson. Imaging 7, 873-879
(1997).

84. Mathews VP, King JC, Elster AD, Hamilton CA. Cerebral infarction: effects of
dose and magnetization transfer saturation at gadolinium-enhanced MR imaging.
Radiology 190, 547-552 (1994).


108. Sepponen RE, Tanttu JI, Suramo I. $T_{1\rho}$ and $T_{1\rho}$ dispersion imaging in patients with cerebral infarction. Society of Magnetic Resonance in Medicine, Books of abstracts, Fifth Annual Meeting, 1986. Montreal, Canada.


112. Tanttu JI, Sepponen RE, Sipponen JT, Heiskanen J. Tissue parameters $T_1$, $T_2$, $T_{1\rho}$ and $T_{1\rho}$ dispersion measured at 0.02 T. Society of Magnetic Resonance in Medicine, Books of abstracts, Fifth Annual Meeting, 1986. Montreal, Canada.


