Magnetization transfer imaging of multiple sclerosis

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While conventional magnetic resonance imaging (MRI) measures signal primarily from the hydrogen nuclei of water, magnetization transfer (MT) MRI indirectly detects macromolecular associated hydrogen nuclei via their magnetic interaction with the observable water. In the normal adult CNS, white matter exhibits the largest MT effect due to the macromolecular content of the highly structured and lipid rich myelin. Pathologies which alter the structural integrity and the relative macromolecular-water composition, such as multiple sclerosis (MS), therefore show abnormal MT. Conventional MRI, which has a high MS lesion detection sensitivity but poor specificity in terms of differentiating the pathological state of a plaque, can thus be supplemented by MT to provide more specific information on the extent of demyelination and axonal loss. In this paper we review the basic concepts of MT imaging and its role in MS lesion characterization.

Key Words: Magnetic resonance imaging — Cross relaxation — Magnetization transfer — Tissue relaxation — Multiple sclerosis — White matter disease.

Introduction

The hydrogen nuclei (protons) of water are the main source of signal in conventional magnetic resonance imaging (MRI) since they exists in abundance, have a high MR sensitivity, and have relaxation times sufficiently long (>~10 ms) to permit easy detection. Image contrast is therefore dependent upon the water content (proton density), characteristic spin-lattice (T1) and spin-spin (T2) relaxation times, and imaging sequence parameters. Macromolecular protons, such as those associated with the lipids of white matter, have extremely short T2s (<~100 μs) and decay completely before they can be measured on an MRI scanner. This population of semi-solid hydrogen nuclei are thus MRI invisible. However, magnetic interactions between semi-solid and water protons results in an exchange of magnetization between the two populations [7, 11]. This magnetization transfer (MT) processes is exploited in MT imaging to indirectly detect the size of the semi-solid magnetization pool and the strength of interaction with the liquid pool. For multiple sclerosis (MS), conventional MRI techniques have demonstrated high detection sensitivity, based primarily upon enhancement on T2-weighted images, but poor specificity in terms of differentiating the pathological state of plaques [38, 27]. Preliminary results in animal models [4] and humans [12, 15, 37] indicate that MT might provide a means of discriminating between inflammation and edema, which result in T2 prolongation of the water pool, and the chronic changes of demyelination and axonal loss, associated with clinical disability [27], that should be reflected in macromolecular pool variations. MT imaging might therefore significantly enhance the utility of MRI in measuring specific pathological features of MS and hence improve its ability to monitor disease load and progression in therapeutic trials.

Theory of magnetization transfer

Magnetization transfer (MT) is the nuclear magnetic resonance (NMR) phenomenon in which spins in two or more distinct environments exchange their magnetization via through-space magnetic interactions or chemical exchange [7, 11, 13]. In a two-pool tissue model, protons may exist in a highly mobile liquid state associated with water or in semi-solid macromolecular sites, of relatively restricted motion, such as cell membranes [39]. The exchange of spin-energy (cross relaxation) across the water-macromolecular phase boundary is believed to involve three steps [7]: 1. rapid chemical exchange between bulk water and water bound at the macromolecular interface (hydration layer); 2. magnetization exchange between the bound water protons and protons at the periphery of the macromolecule via dipolar coupling; and 3. transfer of magnetization from the surface protons to the other macromolecular protons via spin diffusion and cross relaxation (see Figure 1). Since the bulk water and hydration water are considered to be in a state of rapid
Fig. 1. The two-pool tissue model of magnetization transfer. Hydrogen nuclei (H, protons) exist in a highly mobile liquid state associated with water or in semi-solid macromolecular sites of relatively restricted motion. Rapid exchange (diffusion) occurs between bulk water and water bound at the macromolecular interface (hydration layer). Magnetization is exchanged between the bound water protons and protons at the periphery of the macromolecule via dipolar coupling (magnetization transfer, cross-relaxation) and is then distributed to the other macromolecular protons.

chemical equilibrium, they are modeled as single pool of magnetization. In addition to MT, the individual magnetization pools relax to their equilibrium state via other T1 and T2 processes. The difference in mobility (correlation time) between a water molecule and a macromolecule results in the liquid protons having a relatively long T2 (>~ 10 ms) and the semi-solid spins having a very short T2 (<~ 100 μs). Therefore, the pools are characterized by narrow (<~ 100 Hz) and broad (>~ 10 kHz) resonances respectively (see Figure 2). In conventional imaging experiments, the semi-solid magnetization pool is not directly observed since minimum echo times (TE) are at least order of magnitude longer than the T2 or the semi-solid pool. However, exchange between the pools affects the observed bulk water T1 relaxation time.

Magnetization transfer imaging

In an MT imaging experiment a specially designed RF excitation pulse is used to selectively saturate the semi-solid magnetization while leaving the bulk water magnetization unaffected. In tissue undergoing cross-relaxation this saturation is transferred from the semi-solid spins to the water spins. The result is a decrease in water magnetization and apparent T1 relaxation time. In tissue without a significant semi-solid component, such as cerebrospinal fluid, the water magnetization is unaffected. Thus an image acquired with selective saturation of the semi-solid spins (i.e. MT saturation) shows an additional form of contrast that is a function of the relative water/semi-solid pool size, the strength of interaction, and individual pool relaxation times. MT imaging was first demonstrated by Wolff and Balaban who used animal spectrometers and the continuous wave (CW) saturation transfer technique to study rabbit kidney and skeletal muscle in vivo [39]. The CW technique, illustrated in Figure 2a, selectively saturates the semi-solid spins by continuously irradiating at several kHz off-resonance (i.e. below the Larmor frequency for H). This affects the entire semi-solid resonance without disturbing the narrow water resonance. In addition to producing contrast due to cross relaxation, which they termed magnetization transfer contrast (MTC), they assumed complete and exclusive saturation of the semi-solid spins and performed quantitative cross-relaxation experiments [9]. However, since most clinical imagers do not have a decoupler channel, hardware modifications involving the addition of a second RF amplifier must be performed to allow true CW imaging experiments. In addition, the power deposition in a CW experiment can be prohibitive for human imaging at high field strengths (e.g. 1.5T) [35]. The majority of MT imaging to date has been performed using shaped RF pulses that produce a bandwidth of excitation ~ 0.5-10 kHz off-resonance (Figure 2b) [28, 33, 35]. These pulse are used to periodically (partially) saturate the semi-solid magnetization and